

**MEDICAL REHABILITATION:
THE EFFECTS OF AQUATIC PHYSIOTHERAPY IN
PATIENTS WITH RHEUMATOID ARTHRITIS**

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ABSTRACT

Background: Hydrotherapy is frequently indicated in the management of rheumatoid arthritis (RA) patients. Few randomised controlled trials (RCTs) have investigated the effects of hydrotherapy in RA and their findings are inconclusive.

Aims: The aim of this thesis was to evaluate the difference in outcomes (including physical function, quality of life, disease activity, psychological wellbeing and cost) between a 6-week course of hydrotherapy compared to land-based therapy for patients with RA.

Methods: Forty-three patients (mean age = 60 years; SD = 15.3) diagnosed with RA were randomly assigned into either a hydrotherapy plus home exercise (n = 21) or land based therapy plus home exercise group (n = 22). Hydrotherapy included a weekly 45 minutes session for six weeks in addition to a home-exercise programme. Land-therapy included weekly 45 minutes sessions over six weeks plus home-exercise therapy. Patients were assessed at baseline (Test 1); six weeks (Test 2), three months (Test 3), and six months (Test 4) post-treatment. The Primary outcome measured was functional ability using the Health Assessment Questionnaire-Disability Index (HAQ-DI). Secondary outcomes, including HAQ_{VAS} (pain scale), HAQ-GWB (general wellbeing), HRQoL using the EQ-5D_{VAS}, EQ-5D tariff, EQ-5D profile and Quality Adjusted Life Years (QALYs) were calculated. Disease Activity was measured using RA Disease Activity Index (RADAI) and Disease Activity Score 28 (DAS28). Hospital Anxiety and Depression Scale (HADS) was used to measure psychological wellbeing. Costs to the provider (NHS), society and patient were also collected.

Results: Change scores were calculated for all outcome measures between Test 1 and 2; Test 1 and 3; Test 2 and 3 and were used for data analysis. Patients treated with hydrotherapy experienced improvement in functional ability (HAQ-DI; $p < 0.001$), pain (HAQ_{VAS}; $p < 0.001$), general wellbeing (HAQ-GWB; $p < 0.001$), HRQoL (EQ-5D_{VAS}; $p = 0.021$), psychological wellbeing (HADS; $p = 0.023$). Moderate correlation was found in all RA patients between the RADAI and DAS28 ($r = 0.328$, $p = 0.032$). Moderate correlation was found between depression score (HAD-D) and RADAI ($r = 0.578$, $p < 0.001$); there was also moderate significant correlation between anxiety score (HAD-A) and RADAI ($r = 0.425$, $p = 0.005$). Predictors of functional disability in patients with RA were RADAI, EQ-5D tariff, GWB, depression score and anxiety score. The characteristics of patients recruited to this study reflected the RA population in Greater Manchester in terms of age, disease duration (DD), gender, body mass index (BMI) and DAS28. Finally, there were no difference between hydrotherapy and land-based treatment in terms of costs to the patient or society, however, when four patients were treated in the pool compared to one patient on land, hydrotherapy was less costly and more effective in improving functional disability.

Conclusions: RA patients in the hydrotherapy group showed significant improvement in physical function, psychological well-being, quality of life and reduced health care utilisation compared to those in the land-therapy group. Group hydrotherapy is also less costly compared to one-to-one treatment on land.

Keywords: Rheumatoid Arthritis, exercise therapy, hydrotherapy, land therapy, aquatic exercise, functional ability, functional disability, physical function, disease activity, psychological well-being, health related quality of life and quality of life.

DEDICATION

This thesis is dedicated to:

My brothers (Jumaa, Mohammad, Satar and Rahman)

My wife Amna

and

My children

Without whom, there would be no point.

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ABBREVIATIONS

ACR: American College of Rheumatology

AIMS: Arthritis impact measurement scale

AIMS-2: Arthritis impact measurement scale version 2

AMED: Allied and complementary medicine

Anti-CCP: Anti-cyclic citrullinated peptide antibody (anti-citrullinated protein)

ANOVA: Analysis of variance

ARA: American Rheumatism Association

AWR: Average wage rate

BC: Before Christ

BDI: Beck Depression Inventory

BMI: Body mass index

BSR: British Society of Rheumatology

CDAI: Clinical disease activity index

CE: Cost effectiveness

CES-D: Centre for Epidemiologic Studies-Depression Scale

CINAHL: Cumulative Index to Nursing & Allied Health Literature

CMFT: Central Manchester Foundation Trust

COX-1 & COX-2: Cyclooxygenase-1 & Cyclooxygenase-2

CRP: C-reactive protein

C/S: Corticosteroids

CVD: Cardiovascular disease

DAS: Disease Activity Score; DAS28: Disease Activity Score 28

DD: Disease duration

DIP: Distal interphalangeal joint

DMARDs: Disease-modifying anti-rheumatic drugs

DoS: Director of studies

EBV: Epstein-Barr virus

ELs: Educational levels

EMBASE: Excerpta Medica Database

ESR: Erythrocyte sedimentation rate

EQ-5D: EuroQoL

Fc: Fragment crystallisable

FMS: Fibromyalgia syndrome

FSQ: Functional status questionnaire

GCP: Good clinical practice

GP: General practitioner

GWB: General wellbeing

HAD-A: Hospital anxiety depression-anxiety;

HAD-D: Hospital anxiety depression-depression

HADs: Hospital anxiety depression scale

HAQ: Health Assessment Questionnaire

HAQ-DI: Health Assessment Questionnaire-Disability Index

HEP: Home-exercise programme

HLA: Human leukocyte antigen

HRQoL: Health-related quality of life

HT: Hypertension

ICC: Intraclass correlation coefficient

ICER: Incremental cost-effectiveness ratio

IgG: Immunoglobulin G

IHD: Ischaemic heart disease

ILAR: International League Against Rheumatism

JIA: Juvenile idiopathic arthritis

JRA: Juvenile rheumatoid arthritis

MACTAR: McMaster-Toronto Arthritis Patient Preference Questionnaire

MCP: Metacarpophalangeal joint

MDT: Multidisciplinary team

MEDLINE: Medical Literature Analysis and Retrieval System Online

MHC: Major histocompatibility complex

MHIQ: McMaster Health Index Questionnaire

MI: Myocardial infarction

MRC: Medical Research Council

MRI: Manchester Royal Infirmary

MS: Morning stiffness

MTX: Methotrexate

NHP: Nottingham Health Profile

NHS: National Health Service

NICE: National Institute for Health and Clinical Excellence

NNT: Numbers needed to treat

NR: Not reported

NSAIDs: Non-steroidal anti-inflammatory drugs

OA: Osteoarthritis

PIP: Proximal interphalangeal joint

PQoL: Perceived Quality of Life Scale

ProQuest: ProQuest Research Library

Pub-Med: PubMed Central

QALY: Quality-adjusted life year

QoL: Quality of life

QWB: Quality of wellbeing scale

RA: Rheumatoid arthritis

RADAI: Rheumatoid arthritis disease activity index

RADAR: Rapid assessment of disease activity in rheumatology

RAI: Ritchie articular index

RAPID 3: Routine assessment of patient index data 3

RAQoL: Rheumatoid arthritis quality of life

RCT: Randomised controlled trial

RF: Rheumatoid factor

ROM: Range of motion

SAARDs: Slow-acting anti-rheumatic drugs

SDAI: Simplified disease activity index

SD: Standard deviation

SF-36: Short Form (36)

SIP: Sickness impact profile

SJC44: 44 swollen joint count

SLAs: Second-line agents

SLE: Systemic lupus erythematosus

SPSS: Statistical Package for the Social Sciences

SRFT: Salford Royal Foundation Trust

TAG: Transport analysis guidance

TB: Tuberculosis

TJC: Tender joint count

TTO: Time trade off

UK: United Kingdom

USA: United States of America

VAS: Visual analogue scale

WHO: World Health Organisation

WOMAC: Western Ontario and McMaster Universities

WBP: Whole body programmes

CHAPTER ONE: INTRODUCTION

1.1 Background to the study

Rheumatoid Arthritis (RA) is defined as a chronic, inflammatory, autoimmune systemic disease with exacerbation and remission (Hochberg et al., 1992; McCarty & Bundy, 2008). RA affects many organs and tissues in the body, although the joints are usually the most severely affected part (Eberhardt et al., 1990; Jacoby et al., 1973; Tehlirian & Bathon, 2008). This disease of unknown aetiology affects all ethnic groups worldwide (Quinn et al., 2004).

The overall prevalence of RA worldwide in the general population is 1-2% (National Institute for Health and Clinical Excellence (NICE), 2009; Symmons et al., 2002; Symmons et al., 1994). Onset of RA is most commonly in the fourth and fifth decades of life with a peak onset between the ages of 35 and 50 years (Symmons et al., 2002; Tehlirian & Bathon, 2008; Waldburger and Firestein, 2008). It affects between 0.5% and 1% of the population, or approximately 400,000 people, in England and Wales; of these, approximately 15% have a severe case of the disease (NICE, 2010). In the United Kingdom (UK), the first study to report prevalence of RA was published in 1961 by Lawrence, who estimated that 1.1% of the population of Leigh and Wensleydale had RA (Lawrence, 1961). On the other hand, Symmons et al. (2002) found that the prevalence of this condition was about 0.8%, and this suggests that approximately 400,000 people in the UK may have RA (Symmons et al., 2002).

The main clinical features of RA are pain, swelling, tenderness and morning stiffness (MS) that are symmetrical in nature and involve small joints of the hands and feet (Jeffery, 2010; Tehlirian & Bathon, 2008). Other large peripheral joints such as knee joints and elbow joints may also be affected as the disease progresses (Jeffery, 2010). The distal interphalangeal joints (DIP) and thoraco-lumbar spine are spared (Tehlirian & Bathon, 2008). Other common features of RA are fever, fatigue, weight loss, limited functional ability, depression and poor self-esteem (Tehlirian & Bathon, 2008; Tinsley, 1997). All of these symptoms play a role in a decreasing range of movement, functional limitation, loss of independence and reduction of quality of life (QoL), which are all important concerns for patients with RA (Bowling, 2003; Quinn et al., 2004). Although RA is associated with severe disability, it may not directly affect mental functioning but it does have an impact on psychological and social well-being (Bowling, 2003). The disease also has a major impact on physical function, QoL and may lead to premature death (Toussirot, 2010).

The course of RA is unpredictable, and its severity varies widely (Jeffery, 2010; Welsing et al., 2001). Periods of exacerbation and remission of disease activity may interchange (Jeffery, 2010; Quinn et al., 2004). If left untreated, this disease leads to progressive joint destruction and deformity, with resultant deterioration in QoL because of functional limitation due to pain and disability, as well as increased health care utilisation (Jeffery, 2010; Quinn et al., 2004). It is estimated that the cost of treating RA in the UK is about £1.3 billion annually (NICE, 2009; NICE, 2010; Pincus & Callahan, 1993). Each year, the direct cost to the National Health Service (NHS) is estimated at £560 million, while the cost to the wider

economy (such as loss of earnings due to ill health) is estimated at £1.8 billion (NICE, 2010; The Comptroller and Auditor General, 2009), whereas the total cost of RA in the UK, together with the indirect costs and the effects of early mortality and lost productivity, have been approximated at between £3.8 and £4.75 billion per year (NICE, 2009).

The treatment of RA is complex because it is a systemic disease that affects any part of the patient's body. Moreover, this disease has a very significant impact on every aspect of the patient's physical, psychological and social activities (Emery, 2006; Oliver & Clair, 2008; Schur & Moreland, 2011). The treatment of RA can be divided into pharmacological, non-pharmacological and sometimes surgical interventions (Emery, 2006; Luqmani et al., 2009; Schur & Moreland, 2011). Non-pharmacological therapy includes different types of therapy such as rest, educational advice, exercise treatment, hot and cold applications, electrical stimulation and occupational therapy (Oliver & Clair, 2008; Schur & Moreland, 2011). Pharmacological medication involves the main four lines of treatment which are Non-Steroidal Anti-inflammatory drugs (NSAIDs), Disease Modifying Anti-Rheumatic Drugs (DMARDs), Cortico-Steroids (C/S) and Biologic drugs (Luqmani et al., 2009; Oliver & Clair, 2008). In patients with a chronic disease such as RA, rehabilitation therapy is recommended in order to maximise the efficacy of pharmacological treatment and improve health status, physical function and QoL (Hammond, 2004; Vlieland & Thea, 2003).

The management of RA aims to control the symptoms, minimise or avoid joint damage and erosions, preserve physical capacity and prevent or delay disability

(Hurley et al., 2002; Oliver & Clair, 2008). This treatment involves a combination of pharmacological, non-pharmacological (rehabilitation therapy) and if necessary surgical intervention (Hurley et al., 2002; Oliver & Clair, 2008).

Exercise programmes have been suggested to be the cornerstone of rehabilitation for RA as they improve function, muscle strength, and general wellbeing (GWB) (Hurkmans et al., 2009; Vliet Vlieland & Van den Ende, 2011). Exercise programmes for patients with RA are often administered via hydrotherapy (Bender et al., 2005; Schrepfer, 2002; Verhagen et al., 2012). Hydrotherapy has been used since the Roman era as a form of exercising in warm water for therapeutic purposes in order to increase range of motion (ROM), muscle strength, physical function, reduction of pain and improvement of QoL (Verhagen et al., 2012). In the UK, rehabilitation professionals generally define hydrotherapy as heated-pool exercise therapy specifically designed for an individual in an attempt to improve neuromuscular and musculoskeletal function (Bender et al., 2005; Bender et al., 2002).

In this thesis, the terms hydrotherapy, aquatic exercise, aquatic therapy and aquatic physiotherapy are used interchangeably to refer to the use of immersion pools, of a variety of depths, that help the application of various established therapeutic interventions, such as stretching, strengthening, joint mobilisation, balance and gait training (HyDAT Team, 2009; Schrepfer, 2002). In the literature, there is a lack of clarity regarding the differences between hydrotherapy and the terms balneotherapy/whirlpool therapy, spa therapy, thalassotherapy, Kneipp therapy and hydrokinesiotherapy. It is important to recognise the difference

between these modalities (Bender et al., 2005). Although hydrotherapy and balneotherapy are sometimes used interchangeably in the literature, hydrotherapy is accessible to health care professionals and is used in the UK. As such, only the terms hydrotherapy, aquatic exercise, aquatic therapy and aquatic physiotherapy are used in this thesis. Other water-related definitions are described in chapter three (p.67-68).

1.1.1 Hydrotherapy

Hydrotherapy is sometimes used in the treatment of RA by utilising the buoyancy, assistance and resistance of warm water to relieve pain, inducing muscle relaxation, relieving stress on weight bearing joints and promoting more effective exercise (Eversden et al., 2007; Hall et al., 1996; Schrepfer, 2002). Although hydrotherapy is used for RA patients including children or adults age groups, little scientific evidence exists to support the use of this mode of treatment (Hackett et al., 1996). The definitive effectiveness of hydrotherapy on functional ability and QoL in RA patients is inconclusive (Beardmore, 2008; Eversden et al., 2007; Verhagen et al., 2012).

Unblinded studies examining the efficacy of hydrotherapy in RA patients have shown some improvements in pain, Quality of Life (QoL), muscle strength, aerobic conditioning and physical functioning (Danneskiold-Samsoe et al., 1987; Hart et al., 1994; Suomi & Collier, 2003). However, the findings and generalisability of these studies are limited because of the small sample sizes, lack of randomisation, poor allocation concealment and lack of a controlled intervention. A small number of inconclusive studies have investigated the effects

of hydrotherapy in RA with none evaluating the effects on QoL, anxiety and depression, cost-effectiveness (CE) or observing the simultaneous effect on physical function and RA disease activity. To date, the effectiveness of hydrotherapy on functional ability, QoL, depression and anxiety has not been adequately examined in patients with RA, and the cost-effectiveness of hydrotherapy for patients with RA is unknown.

1.2 Study aims

The aims of this thesis are divided into primary and secondary.

1.2.1 Primary aim

The primary aim of the present study was to:

- Evaluate the difference in outcomes for RA patients when treated with hydrotherapy as opposed to land-based therapy.

1.2.2 Objectives

The secondary aims of the present study were to:

- Determine the effect of hydrotherapy in the management of patients with RA by conducting a systematic review.
- Identify and evaluate the differences in demographic factors between the hydrotherapy and land-therapy groups.
- Identify and understand the reasons for the difference in functional ability measured by Health Assessment Questionnaire-Disability Index (HAQ-DI) between those receiving hydrotherapy and those having land therapy.
- Evaluate if hydrotherapy could improve pain and GWB; health related quality of life (HRQoL); disease activity; mood symptoms (depression and anxiety) more effectively than land therapy in patients with RA.

- Determine the association between variables measuring disease activity.
- Determine the association between variables measuring psychological status with socio-demographic features and disease activity indices.
- Determine which factors predict functional disability.
- Describe and compare patient characteristics from Study One with patients from a regional rheumatology centre and previous rheumatology studies.
- Evaluate the cost of hydrotherapy compared to the land-based treatment, from the viewpoint of the provider [NHS], patient and society.

1.3 Hypothesis

H₀: There will be no significant difference in HAQ-DI score between hydrotherapy and land-therapy arms in patients with RA.

H₁: There will be a significant difference in HAQ-DI score between hydrotherapy and land-therapy arms in patients with RA.

This study was divided into three major sections:

Study One (43 RA patients): Investigated the clinical effectiveness of hydrotherapy plus home exercises vs. land therapy plus home exercises for patients with RA using RCT.

Study Two (200 RA patients): Examined RA patients' pathway in Greater Manchester from a collected data sample of 10% of all RA patients in the Greater Manchester using descriptive statistics to compare it with the RCT Study One and other comparator literature rheumatology studies.

Study Three (36 RA patients): Examined the cost-effectiveness of hydrotherapy compared to land therapy in RA patients.

1.4 Outline of thesis

Section 1.2 has defined the aims of the thesis, and **section 1.3** has described the hypothesis on which the thesis is based. The rest of the thesis is structured as follows:

Chapter 2 describes the background of RA in terms of the definition, epidemiology, anatomy, pathogenesis, diagnostic criteria, clinical features and management. Study of the more comprehensive details has attempted to determine the type of treatment (pharmacological or non-pharmacological) suitable for management of RA patients.

Chapter 3 provides a detailed description of hydrotherapy in terms of definitions, history, physical property of water, indications, and contraindications.

Chapter 4 critically evaluates the effectiveness of hydrotherapy in RA patients using a systematic review of the updated available literature. The results of this chapter are based on the previously published papers.

Chapter 5 discusses the methodology, illustrating the study design as well as the intervention, development and application of the treatment protocol prescribed to the intervention groups (RCT Study One). It also describes the preparations carried out prior to data collection; patient sample; patient recruitment process; a rationale for the choice of outcome measures and planned data analysis.

Chapter 6 describes the results and overall summary of findings from Study One.

Chapter 7 presents data from the RCT and compares it with general RA data of Kellgren rheumatology centre (Study Two) and some data from the literature.

Chapter 8 evaluates the cost and CE of hydrotherapy compared to land therapy from the perspective of the healthcare provider, patient and society (Study Three).

Chapter 9 ‘Discussion’: The findings from all the three studies are discussed.

Chapter 10 contains ‘Summary, conclusions, clinical implications and recommendations’ from the present research, including the strengths, limitations, key learning, methodological quality and economic evaluation. Suggestions for future studies are also highlighted.

1.5 Summary

RA is an intermittent, sporadic condition of unknown cause; that may affect any age group. It is accepted that RA is a chronic progressive disease in most cases, if not particularly managed appropriately; it can progress to cause joint damage and disability. This may result in a wide range of complications for people with the disease, which can influence their QoL and occupations, and may increase cost to the NHS and society in general. Deciding on a particular type of treatment for RA patients is a major role and is a challenge to reduce the inflammation, relieve pain and stiffness, and control signs and symptoms. The decision of which treatment strategy to choose is valuable in that it could prevent further damage to the joint or irreversible disability, and that it could preserve the body from permanent damage, thus permitting the patient to live the life style they desire.

The next chapter presents the definition, epidemiology, anatomy, pathogenesis, diagnostic criteria, clinical features and management of RA.

CHAPTER TWO: RHEUMATOID ARTHRITIS:

BACKGROUND

2.1 Introduction

One of the most common rheumatic diseases is RA, named in 1859 by Garrod (Garrod, 1876). RA is a chronic, inflammatory, deforming, destructive and systemic disease that can be exacerbated and can go into remission. The objective of this chapter is to provide an overview of RA – including its definition, diagnostic criteria, anatomy, pathophysiology and the epidemiology of the disease; it also discusses the clinical features of RA and the pharmacological and non-pharmacological management.

2.2 Definitions and clinical features

RA is a chronic, inflammatory, symmetrical polyarthritis systemic disease that can be erosive and deforming (Hochberg et al., 1992; Mitchell et al., 2005). This disease is characterised by joint pain, swelling, tenderness and the destruction of synovial joints, leading to severe disability and premature mortality (Mitchell et al., 2005; Wolfe et al., 2005).

RA courses are classified into early, established and late (Jacoby et al., 1973; Shipley et al., 2005). It typically affects the small joints of the hands as well as wrists, knees, ankles, elbows, shoulders and feet (Tehirian & Bathon, 2008; Temprano & Smith, 2011). The thoraco-lumbar spine, distal interphalangeal joint (DIP) and hips are often not affected (Tehirian & Bathon, 2008; Temprano &

Smith, 2011). The hallmark symptom of RA is symmetrical joint pain and MS lasting more than an hour (Tehirian & Bathon, 2008). Sleep may be disturbed and the patient feels permanently tired and generally unwell (Shipley et al., 2005) contributing to fatigue (Pinals et al., 1981).

Fatigue is the most common complaint among RA patients (Schur & Moreland, 2011) and one of the key factors leading to decreased QoL (Swain, 2000). More than 70% of RA patients have fatigue and it is more severe and frequent than pain (Wolfe et al., 1996). Many aspects might influence the impact of fatigue such as physical, psychological and social functioning (Trendall, 2000).

It has been suggested that one of the main limitations of clinical trials is that fatigue is rarely identified as one of the core outcomes and therefore is rarely addressed as a treatment target in its own right, dissimilar to pain and functional disability (Felson et al., 1993). However, multifactorial agents influence RA fatigue, such as the inflammatory process of RA, personal life issues, and cognitive and behavioural issues (Hewlett et al., 2011). RA inflammatory processes cause fatigue by different mechanisms. Pain, poor sleep, muscle effort (resulting from joint damage and reduced physical activity), anaemia and RA medication, all might cause fatigue in RA (Hewlett et al., 2011). Personal factors that potentially influence RA fatigue are related to personal responsibilities in terms of caring for family members, going to work to earn an income, difficult personal environments (e.g. stairs, lack of assistive devices) and a lack of social support (Hewlett et al., 2011). Cognitive behavioural factors such as thoughts, feelings, low mood and low self-efficacy might also influence fatigue. These

multiple causes of fatigue should be taken in to account when considering management (Hewlett et al., 2011).

The clinical course of RA is one of exacerbations and remissions (McMahon & Allard, 2002; Temprano & Smith, 2011). Before the use of biologics drugs, it appears that about 20-25% of sufferers had mild cases of RA; approximately 50% of patients were very limited and became unable to work 10-years post- diagnosis, and 20-25% had severe joint damage and early mortality caused by complications of RA, such as cardiovascular diseases (CVDs) (Gordon & Hastings, 2004; MacAuley, 2007; McMahon & Allard, 2002; Temprano & Smith, 2011). However, these percentages have improved greatly recently due to the efficacy of biologic drugs (Arthritis Research UK, 2011; Singh et al., 2009).

The majority of RA patients 75% have some damage to joints, swellings and flare-ups, some 20% have mild symptoms causing few problems, and some 5% develop severe conditions with extensive disability (Arthritis Research UK, 2011; Mitchell et al., 2005). The factors associated with poor prognosis are positive rheumatoid factor, female gender, Human leukocyte antigen-DR4 (HLA-DR4), extra-articular features, severe disability at presentation and insidious onset (Hochberg et al., 2004; Mitchell et al., 2005; Tehlirian & Bathon, 2008). Disease onset can take many forms. RA results in peripheral poly arthritis and has detrimental psychological consequences for patients (Mella et al., 2010). Thus, severe pain, functional incapacity, fatigue, economic restrictions and the side-effects of medication may lead to decreased QoL and are associated with

biopsychosocial problems and psychological symptoms such as anxiety and depression (Mella et al., 2010; Pollard et al., 2005).

Longitudinal studies have reported variables that are associated in patients with RA including exacerbation of disease activity, radiological damage, impaired QoL and functional disability (Paget, 2007; Ward, 2007). These variables are closely inter-linked and may increase the burden in patients with RA (Scott et al., 2000; Scott et al., 2003). Disability is a major factor, which contributes to dependency on others for activities of daily living; decrease in social interaction; and early retirement due to ill health in patients with RA. In addition, studies have reported that increased physical disability was associated with psychological status, educational levels (ELs), employment, social support and presence of comorbidity (Lillegraven & Kvien, 2007). Furthermore, about 10% of RA patients are most likely to suffer from severe joint damage within two years of disease onset, leading to substantial increased functional disability (Paget, 2007; Morel & Combe, 2005).

2.3 Diagnostic criteria of rheumatoid arthritis (RA)

The diagnosis of RA depends on specific criteria as stated (Table 2.1, p.33). RA must be differentiated from other rheumatic diseases, such as osteoarthritis (OA), systemic lupus erythematosus (SLE) and other sero-negative spondyloarthropathy, which can have similar clinical features (Akil & Amos, 1995a; Arnett et al., 1988; Arnett et al., 2005; Temprano & Smith, 2011). A person can be classified as having RA if > 4 criteria are present at any time. The criteria method is a practical

way for making a diagnosis, also it may aid the differential diagnoses from other rheumatic diseases (Arnett et al., 1988; Arnett et al., 2005).

Table 2.1: 1987 revised American College of Rheumatology (ACR) criteria for the classification of RA (“Reproduced from Arnett et al., 1988, with kind permission of John Wiley and Sons, Inc.”).

Criteria item	Definitions
1	Stiffness in and around the joints lasting > one hour before maximal improvement
2	Arthritis of > three joints, simultaneously
3	Arthritis of the proximal interphalangeal (PIP), metacarpo-phalangeal (MCP) & wrist joints
4	Symmetrical arthritis
5	Rheumatoid nodules
6	A positive test for serum rheumatoid factor/might be positive in other rheumatic diseases such as systemic lupus, psoriatic arthropathy
7	Radiographic changes, characteristic of RA (erosion and/or periarticular osteopenia in hand and/or wrist joints. It would take three years for the erosion to be seen by X-ray

Recently, the ACR/European League against Rheumatism developed a new set of criteria for classification of RA (Aletaha et al., 2010) (Table 2.2, p.34). Application of these new criteria provides a score of 0-10, a score of > six being indicative of the presence of definite RA (Aletaha et al., 2010).

Table 2.2: 2010 American College of Rheumatology/European League against Rheumatism classification criteria for RA (“Reproduced from (Aletaha et al., 2010), with kind permission of John Wiley and Sons, Inc.”).

A. Joint involvement	Score
<ul style="list-style-type: none"> • 1 large joint • 2-10 large joints • 1-3 small joints (with or without involvement of large joints) • 4-10 small joints (with or without involvement of large joints) • >10 joints (at least 1 small joint) 	<p>0</p> <p>1</p> <p>2</p> <p>3</p> <p>5</p>
B. Serology (at least 1 test result is needed for classification)	Score
<ul style="list-style-type: none"> • Negative RF and negative anti-CCP • Low-positive RF or low-positive anti-CCP • High-positive RF or high-positive anti-CCP 	<p>0</p> <p>2</p> <p>3</p>
C. Acute-phase reactants (at least 1 test result is needed for classification)	Score
<ul style="list-style-type: none"> • Normal CRP and normal ESR • Abnormal CRP or abnormal ESR 	<p>0</p> <p>1</p>
D. Duration of symptoms	Score
<ul style="list-style-type: none"> • < 6 weeks • ≥ 6 weeks 	<p>0</p> <p>1</p>
<p>Key:</p> <p>Anti-CCP: Anti-cyclic citrullinated peptide antibody (anti-citrullinated protein)</p> <p>CRP: C-reactive protein</p> <p>ESR: Erythrocyte sedimentation rate</p>	

2.4 Epidemiology of rheumatoid arthritis (RA)

The most common form of inflammatory arthritis is RA; it affects 1-2% of the population in all racial groups and 0.5–1% of the UK population (Alamanos & Drosos, 2005; Riise et al., 2000; Symmons et al., 2002).

In the UK, there are 100 new cases of inflammatory joint disease per hundred thousand people per year, of whom 24 would have RA (Riise et al., 2000; Söderlin et al., 2002; Symmons et al., 2002). In England and Wales, RA affects between 0.5% and 1% of the population, or approximately 400,000 people; approximately 15% of these have severe disease (NICE, 2010). In the United States of America (USA), the average annual incidence of RA is 0.5 per 1000 persons' per year (Drosos, 2004).

The disease occurs more frequently in women, the female to male ratio being 4:2, and it may start at any age (Tehirian & Bathon, 2008; Temprano & Smith, 2011; Waldburger & Firestein, 2008). The consensus is that RA affects individuals during the fourth and fifth decades of life with peak onset between the ages of 35 and 50 years (Drosos, 2004; Symmons et al., 2002). Almost half the people with RA are of working age, and > 60 % have had the disease for more than ten years (Wolfe & Hawley, 1998). One third of people will have stopped working within two years of diagnosis (NICE, 2009). This potential disabling disease has a significant impact on QoL, with job loss resulting in increased healthcare costs to the community (Lerner et al., 2005).

Figure 2.1 (p.37) and Table 2.3 (p.38) summarise the prevalence of the worldwide population of RA. There is no general agreement on the prevalence of RA. Studies in Asia and the Far East (Dans et al., 1997; Shichikawa et al., 1999; Zeng et al., 1997) report low rates of incidence – approximately 0.3%, 0.2% and 0.17% respectively. Conversely, significantly higher prevalence is reported in some native American-Indian populations as shown by Del Puente et al. (1989) (5.3%) and by Harvey et al. (1981) (6.8%); the reason for these findings can probably be related to the poorly defined genetic factors (Waldburger & Firestein, 2008). The estimated prevalence of RA is relatively constant, between 0.5% and 1%, as shown in European RA population studies – Symmons et al. (2002) (UK); Carmona et al. (2002) (Spain); Riise et al. (2000) (Norway); Kvien et al. (1997) (Norway); Power et al. (1999) (Ireland); Neovius et al. (2011) (Sweden); Adomaviciute et al. (2008) (Lithuania) and Aho et al. (1998) (Finland). This finding is similar to North American RA population studies Gabriel et al. (1999) and Gabriel (2001); and studies in developing countries Al-Rawi et al. (1978) (Iraq); Pountain, (1991) (Oman).

There are several possible explanations for the discrepancy in the data reported on the prevalence rate among RA studies:

- The authors used different diagnostic criteria and cut-off points.
- RA patients of different ages were studied and this may have affected their findings; some studies used 15 years as minimum for RA adult age (Cimmino et al. 1998, Pedersen et al. 2011 and Symmons et al. 2002) whereas other studies (Riise et al. 2000) used 18 or 20 years as a minimum adult age.

- Participants presented in Figure 2.1 (p.37) and Table 2.3 (p.38) were recruited from different populations with a variable sample size (range 227-356,000).
- The inclusion and exclusion criteria and method of participant recruitment were not stated in other studies such as Zeng et al. (1997); Kvien et al. (1997).

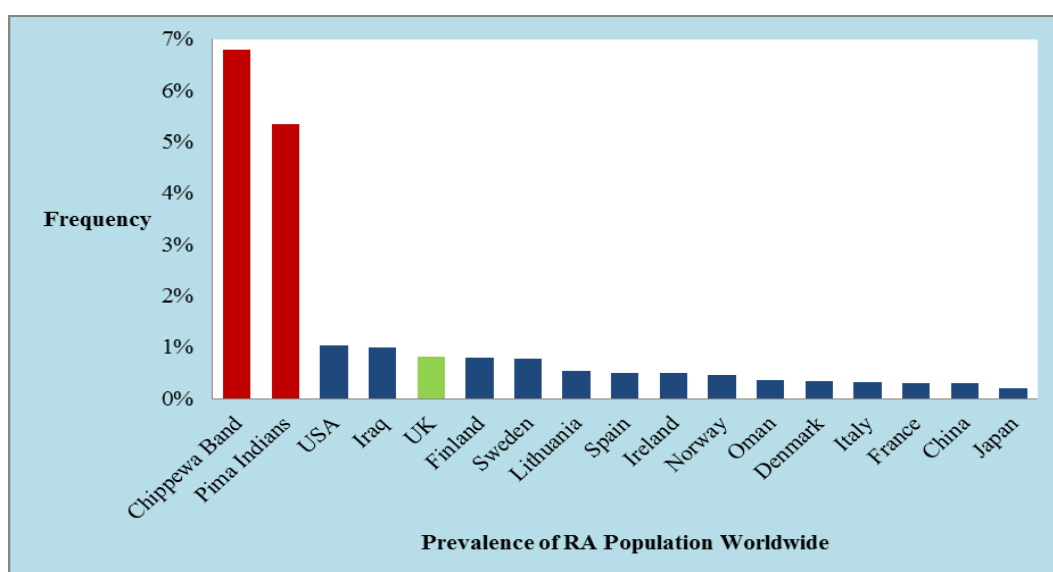


Figure 2.1: Prevalence of RA worldwide. Data were taken from Harvey et al. (1981); Del Puente et al. (1989); Gabriel et al. (1999); Al-Rawi et al. (1978) Symmons et al. (2002); Aho et al. (1998); Neovius et al. (2011); Adomaviciute et al. (2008); Carmona et al. (2002); Power et al. (1999); Kvien et al. (1997); Pountain (1991); Del Puente et al. (1989); Pedersen et al. (2011); Cimmino et al. (1998); Guillemin et al. (2005); Zeng et al. (1997); Shichikawa et al. (1999).

No nation is spared and the geographical distribution of the disease is remarkably homogeneous with a few exceptions such as the Far East Figure 2.1 (p.37) and Table 2.3 (p.38). In all population studies, the marked female excess remains unexplained.

Table 2.3: Summary of epidemiological studies worldwide.

Authors	Country	Criteria used	Sample size	Age	Total prevalence	Female prevalence %	Male prevalence %
Carmona et al. (2002)	Spain	ACR 1987	2998	≥ 20	0.5%	0.8%	0.2%
Shichikawa et al. (1999)	China	ARA 1961 Rome criteria	3000	NR	0.2%	NR	NR
Zeng et al. (1997)	Japan	NR	22,049	NR	0.32%	0.39%	0.29%
Guillemin et al. (2005)	France	ACR 1987 + clinical examination by rheumatologists	9395	≥ 18	0.31%	0.51%	0.09%
Pedersen et al. (2011)	Denmark	Modified ACR 1987 or ACR 1987	4995	≥ 15	0.35%	0.46%	0.24%
Del Puente et al. (1989)	Pima Indians of Arizona/ USA	ARA & modified ACR 1987	3,868	≥ 20	5.3%	6.95%	3.23%
Harvey et al. (1981)	Central Minnesota, USA	NR	227	NR	6.8%	NR	NR
Symmons et al. (2002)	UK	ACR 1987	6000	≥ 16	0.8%	1.16%	0.44%
Riise et al. (2000)	Norway	ACR 1987	100,000	≥ 20	0.39% (1989) 0.47% (1994)	0.54% (1989) 0.63% (1994)	0.24% (1989) 0.30% (1994)
Cimmino et al. (1998)	Italy	ACR 1987	4456	≥ 16	0.33%	0.51%	0.13%
Kvien et al. (1997)	Norway	NR	356,486	≥ 20	0.5-1%	NR	NR
Power et al. (1999)	Ireland	ARA criteria 1987	2,500	NR	0.5%	NR	NR
Neovius et al. (2011)	Sweden	NR	96 560	≥ 16	0.68%	1.11%	0.43%
Adomaviciute et al. (2008)	Lithuania	NR	6542	NR	0.55%	NR	NR
Aho et al. (1998)	Finland	NR	100,000	> 30	0.8%	NR	NR
Gabriel et al. (1999)	Rochester, Minnesota, USA	ACR 1987	425	≥ 30	1%	NR	NR
Dans et al. (1997)	Filipino	ACR criteria 1987	3065	NR	0.17%	NR	NR
Al-Rawi et al. (1978)	Iraq	ARA criteria 1957	6999	≥ 16	1%	NR	NR
Pountain (1991)	Oman	ARA criteria 1987	1925	≥ 16	0.84%	NR	NR
Key:							
ACR: American College of Rheumatology; ARA: American Rheumatism Association; NR: Not reported							

2.5 Risk factors for rheumatoid arthritis (RA)

RA is considered as a heterogeneous disease with variable severity and unpredictable response to therapy. There are many risk factors predisposing to RA occurrence. Different risk factors will be discussed below.

2.5.1 Genetic factors

These contribute to the disease susceptibility through a genetic basis (Kelley & Kimberly, 2008; Silman & Pearson, 2002; Tobón et al., 2010). In first-degree relatives, the risk of developing RA is approximately 1.5-fold higher than the general population (Kelley & Kimberly, 2008; Lawrence, 1970; Lawrence & Ball, 1958; Tobón et al., 2010). Arthritis Research UK stated in 2011 that the disease may run genetically in some families, but that the method of inheritance is not transferred directly to individuals who carry the defective gene, but that it might increase the susceptibility of developing RA.

The most potent genetic risk factor for RA is related to major histocompatibility complex alleles (MHC) or human leukocyte antigen (HLA) when peptides are bound and can be recognised by T-cells; the commonest T-cell is the HLA DRB1 alleles (Barton & Worthington, 2009; Silman & Pearson, 2002). Only 50% of the genetic contribution to RA can be explained by HLA, while others related to polymorphisms may play a role in RA for the incremental risk (MacGregor et al., 2000; Tobón et al., 2010).

2.5.2 Non-genetic risk factors

Non-genetic risk factors describe all susceptible factors implicated with RA disease without an obvious genetic basis (Silman & Pearson, 2002; Tobón et al.,

2010). Investigations into the role of hormones and pregnancy in RA have been made to try to discover what factor influences the higher number of women affected with RA (2 to 4 times more than men) (Barrett et al., 1999; Silman, 1994; Symmons et al., 2002). Hormones such as oestrogen or progesterone could potentially explain some of this gender inequality (Klareskog et al., 2006; Temprano & Smith, 2011; Tobón et al., 2010). The development of RA disease is alleviated by oestrogen and pregnancy, while SLE tends to flare during pregnancy and in response to oestrogen (Ostensen, 1999). Exogenous hormonal effects are also implicated in disease risk (Silman & Pearson, 2002; Silman, 1994; Symmons et al., 2002; Tobón et al., 2010). There have been several studies affirming that adult females taking the oral birth-control pill were at less risk of developing RA (Brennan et al., 1997; Doran et al., 2004; Silman, 1994; Symmons et al., 2002; Tobón et al., 2010).

Numerous studies have attempted to explain the association between RA and other comorbidities such as thyroid diseases and diabetes, which present an increased frequency in both diseases and in their families (Silman & Pearson, 2002; Tobón et al., 2010). Other research studies confirmed that there might be a common genetic link between RA, autoimmune thyroid disease and insulin-dependent diabetes (Myerscough et al., 2000; Silman, 1994; Silman & Pearson, 2002; Tobón et al., 2010). The significance of these findings is yet unclear. One conclusion might be that endogenous or exogenous hormones may postpone, rather than totally protect against, the development of RA.

2.5.3 Environmental factors

The term environment is frequently used to describe all those susceptibility factors implicated in RA that are based on a recognisable genetic marker, but are unexplainable (Silman & Pearson, 2002; Tobón et al., 2010). Tobacco smoking is the best example of exposure to environmental factors; several studies have shown that cigarette smoking is associated with an increased risk of RA (Hutchinson et al., 2001; Papadopoulos et al., 2005; Symmons et al., 2002; Uhlig et al., 1999; Tobón et al., 2010). It has been proved conclusively that the strong correlation between RA and smoking increases in patients with positive RF (Silman & Pearson, 2002; Tobón et al., 2010).

Large numbers of infectious diseases such as viruses (Epstein-Barr virus (EBV) and parvovirus) including bacteria (proteus and mycoplasma) have been implicated as risk factors in developing RA (Silman & Pearson, 2002; Tobón et al., 2010). Several observations have suggested a relationship between EBV and RA. Viral products might participate indirectly to inflammatory arthritis in genetically susceptible individuals through stimulation of the immune system (Paget & Routh, 2010; Silman & Pearson, 2002; Tobón et al., 2010).

Diet is another non-infectious environmental factor examined for its significance in RA outcomes (Symmons et al., 2002; Tobón et al., 2010). Some studies show that treatment with Omega3 fatty acid is associated with improvement in some RA outcomes such as diminishing the severity of inflammation (Kremer, 2000; Tobón et al., 2010; Volker et al., 2000). However, it is unclear whether these dietary factors do have a protective role against RA. Although the exact cause for

developing RA is poorly stated, it appears that people with a genetic predisposition who are also exposed to risky environmental factors or significant hormonal imbalance are the most susceptible candidates. Much evidence is available through the interplay of genetic, hormonal, immunological and environmental factors, which act as trigger factors in RA.

2.6 Pathophysiology

The pathogenesis of RA is complex; however, there have been advances in understanding the cellular and molecular mechanisms in chronic inflammation and tissue damage (Gregersen et al., 2005; Harris Jr, 1986; Shipley et al., 2005). The provoking effects in the pathogenesis of RA are thought to be activation of T-cells by an unknown antigen in a genetically susceptible individual, such as first-degree relatives and identical twins (Harris Jr, 1986; Weissmann, 2004; Weyand & Goronzy, 1997). Proliferation of synoviocytes, endothelial cells and other pro-inflammatory cells all occur through activation of the T-cells (Harris Jr, 1986; McInnes & Schett, 2007; Weyand & Goronzy, 1997). The finding of the rheumatoid factor (RF) in the blood of patients with RA has led to the immunological hypothesis of disease pathogenesis (Firestein, 2005; Weissmann, 2004; Weyand & Goronzy, 1997). Since RF is an autoantibody, the concept that RA is an autoimmune disease has gained reliability (Firestein, 2005; Song & Kang, 2010; Weissmann, 2004).

B-cells may contribute to the pathogenesis of RA through production of rheumatoid factor and other autoantibodies (Edwards & Cambridge, 2006; Harris Jr, 1986; Weissmann, 2004). The production of rheumatoid factors (anti-IgG

immunoglobulin) requires the interaction of T- and B-lymphocytes (Firestein, 2005; Weissmann, 2004; Weyand & Goronzy, 1997). RF and anti-cyclic citrullinated peptide antibodies (anti-CCP) with other autoantibodies, which target systemic and synovial auto-antigens, may contribute to the inflammatory response through activation of complement (Firestein, 2005; McInnes & Schett, 2007; Weissmann, 2004; Weyand & Goronzy, 1997).

Although the pathogenesis of RA is incompletely understood, it involves both T and B-lymphocytes as a complex network of cytokines and growth factors offering many different targets for pharmacological intervention. Joint damage in RA starts with the proliferation of synovial macrophages and fibroblasts after a trigger incident, possibly an autoimmune or infectious episode (Firestein, 2005; Weyand & Goronzy, 1997). The initial trigger for the RA pathological changes is unknown, but joint heat and redness caused by increased vascularity to the joint, then proliferation of the synovial membrane with increased synovial fluid, results in severe pain (Firestein, 2005; Weissmann, 2004; Weyand & Goronzy, 1997).

The most common causes of joint pain in RA are:

- Capsular stretching caused by swelling in the joint, leading to stretching of pain receptors (Arthritis Research UK, 2011; NICE, 2009; Waldburger & Firestein, 2008).
- Irritation of nerve endings by the inflammatory chemicals (Arthritis Research UK, 2011; Waldburger & Firestein, 2008).

Wasting of the muscles around the joints has been attributed, at least in part to joint pain, tenderness and swelling leading to loss of joint function. Continuation of the condition will lead to inflammation of the synovial membrane leading to increased joint damage and progressing deformities (NICE, 2009; McInnes & Schett, 2007; Waldburger & Firestein, 2008). Thus, joint pain indirectly causes muscle wasting by the disuse of muscles due to pain and tenderness.

Another cause of muscle wasting is rheumatoid cachexia (Walsmith & Roubenoff, 2002). RA is accompanied by a loss of body cell mass, a metabolic abnormality known as 'rheumatoid cachexia', which predominates in skeletal muscle and occurs in the viscera and immune system (Walsmith & Roubenoff, 2002). Typically, rheumatoid cachexia results from the reduced muscle mass and increased fat mass that occurred in patients with normal or increased BMI (Summers et al., 2010). Currently there is no established mechanism for this phenomenon, but it is attributed to increased production of pro-inflammatory cytokines (mainly tumour necrosis factor- α and interleukin-1 β), elevated resting energy expenditure, and accelerated whole-body protein catabolism (Summers et al., 2010; Walsmith & Roubenoff, 2002). Thus, rheumatoid cachexia in RA leads to muscle weakness and a loss of functional capacity and is believed to accelerate morbidity and mortality (Walsmith & Roubenoff, 2002).

Inflammatory processes sometime spread to the tendon sheath, which leads to tendon rupture (NICE, 2009; Waldburger & Firestein, 2008). The suppression of inflammation in the early stages of the disease can result in improvements in long-term outcomes for joints, muscles, tendons and nerves (NICE, 2009).

To conclude, it is clear that immune disturbances play a key role in susceptibility to RA, and that variation in the same loci may predispose the patient to other autoimmune diseases. It remains unclear as to what determines the pattern, extent, and progression of the disease. In RA, the synovial membrane is the primary target organ to which the main changes occur, and joint inflammation and damage occur through the interconnection between cellular and molecular immunity (Firestein, 2005; Gregersen et al., 2005).

2.7 Anatomy of synovial joints

Understanding how the inflammatory process develops in most autoimmune inflammatory diseases like RA requires the knowledge of how a normal joint works (Arthritis Research UK, 2011). Figure 2.2 and 2.3 (p.46) illustrate the differences between a normal joint and an inflamed joint (Arthritis Research UK, 2011). The cartilage is characterised by its very smooth, slippery surface, which allows an easy frictionless movement of bones (Arthritis Research UK, 2011; NICE, 2009; Waldburger & Firestein, 2008). The capsule that covers the synovium acts as joint stabiliser and prevents excessive bone movement (Arthritis Research UK, 2011; Waldburger & Firestein, 2008).

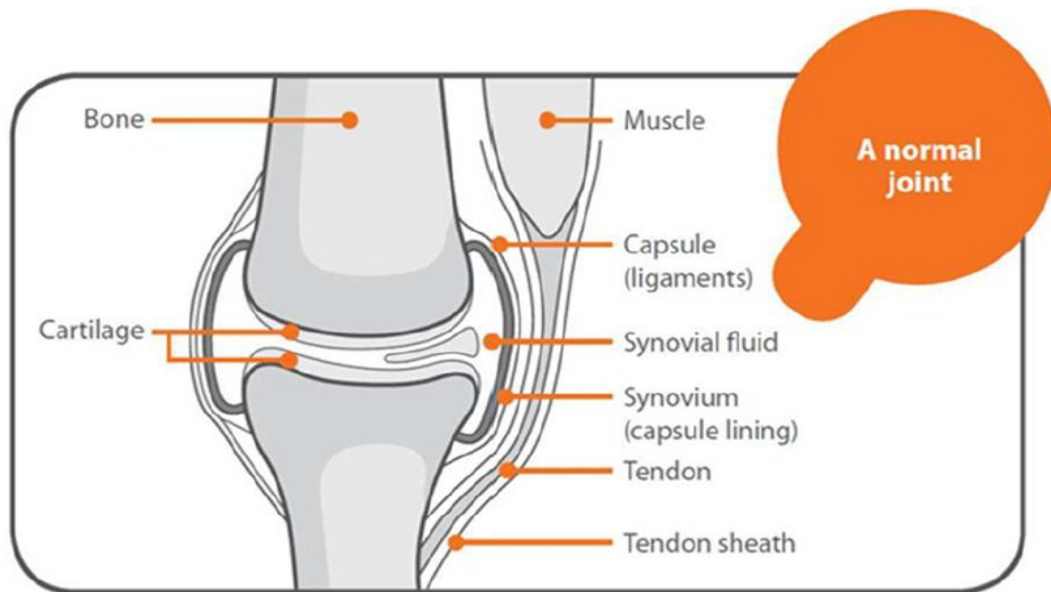


Figure 2.2: Normal joint [Reproduced from Arthritis research UK (2011) with kind permission].

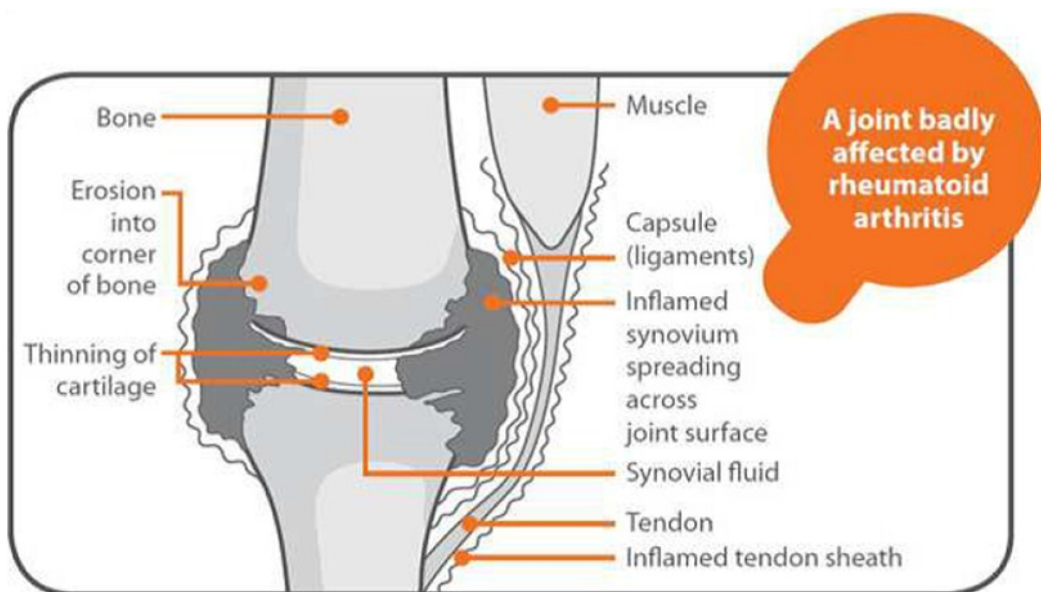


Figure 2.3: RA joint [Reproduced from Arthritis research UK (2011) with kind permission].

2.8 Musculoskeletal and extra-articular manifestations

RA can affect any synovial joint but has a predilection to the small joints of the hands and feet (Cojocaru et al., 2010; McMahon & Allard, 2002). In the early

stages, there is only swelling and inflammation of the affected joint, but deformities occur if the disease is left untreated (Tehirian & Bathon, 2008). Typical deformities include: Radial deviation at wrist, ulnar deviation at MCP joints, dorsal subluxation of MCP, Boutonniere deformities of fingers (with flexion of proximal interphalangeal joints (PIPs) and hyperextension of distal interphalangeal joints (DIPs) resulting from a lack of collateral ligament support), swan-neck deformities of fingers (hyperextension of PIP and flexion of DIP) and Z-deformity of thumb (McMahon & Allard, 2002; Tehirian & Bathon, 2008). There are varieties of soft tissue disorders that may be associated with RA, such as tendon inflammation and tendon rupture (Gordon & Hastings, 2004; McMahon & Allard, 2002).

Other features of RA are fever, fatigue, loss of appetite, weight loss, limited functional ability, depression and poor self-esteem (Jeffery, 2010; Tehirian & Bathon, 2008). These are all important concerns for patients with RA and play a role in decreasing range of movement, functional limitation, loss of independence and reduction of QoL, (Bowling, 2003; Quinn et al., 2004). Any organ in the body (Table 2.4, p.48) may be involved in RA during the illness trajectory (Cojocaru et al., 2010; Gordon & Hastings, 2004; Turesson et al., 2003). These extra-articular manifestations can be seen in 40-50% of RA patients at some point during their lifetime of living with RA (Cojocaru et al., 2010; Tehirian & Bathon, 2008).

Table 2.4: Common extra-articular manifestations of RA (adapted from Tehlirian and Bathon, 2008, with kind permission of Springer Science + Business Media).

System(s) affected	Nature of extra-articular manifestations
Ophthalmology (eye)	Keratoconjunctivitis sicca (dry eyes and dry mouth), episcleritis, scleritis, uveitis, ulcerative keratitis
Neurology (nervous system)	Peripheral entrapment neuropathy, cervical myelopathy due to cervical spine subluxation (rarely)
Cardiac (heart)	Pericarditis, accelerated atherosclerotic disease, valvulitis
Pulmonary (lung)	pleural effusions, pulmonary nodules, diffuse interstitial lung disease, fibrosing alveolitis, caplan's syndrome, cricoarytenoid arthritis (pulmonary arteritis, shrinking lung)
Renal (kidney)	Amyloidosis
Hepatic (liver)	Elevated liver enzymes (non-specific transaminitis)
Spleen	Splenomegaly, Felt's syndrome (neutropenia, large granular lymphocytes, thrombocytopenia)
Skin	Rheumatoid nodules, leg ulcer, nail fold lesions of vasculitis
Muscular	Muscle atrophy, inflammatory myositis
Vascular blood vessels	Small vessel vasculitis, systemic vasculitis, anaemia and lymphadenopathies
Psychosocial (non-specific)	Fatigue, depression, weight loss, cachexia, malaise, fever

2.9 Treatment strategies

RA affects any part of the patient's body, not just the articular and locomotor systems; therefore, the treatment for this disease is complex (Oliver & Clair, 2008; Shipley et al., 2005). Treatment of RA may differ among rheumatologists and currently, clear and consensual international recommendations on RA

treatment are not available (Smolen et al., 2010). Patients need clear explanations and reassurance during the period of diagnosis because diagnosis of RA causes great concern and fear (Arthritis Research UK, 2011; Shipley et al., 2005). Thus, in addition to non-pharmacological and pharmacological therapy, input from the multidisciplinary team (MDT) - including rheumatologist, orthopaedist, nurse, occupational therapist, physiotherapist, social worker and psychologist – is needed (Luqmani et al., 2009; Schur & Moreland, 2011). Moreover, surgical intervention may be required for joint replacement or other surgical procedures in cases of chronic RA (Oliver & Clair, 2008; Shipley et al., 2005).

It is believed that in optimal care of RA, there is no specific standard treatment, but monitoring disease activity outcomes provide a clue to determining if patients need changes in therapy (Luqmani et al., 2009; Oliver & Clair, 2008). The main aim of RA treatment sort by the British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group, are to control synovitis early and effectively, to prevent joint damage, achieve functional ability, maintain employability, improve psychosocial functioning, monitor for drug toxicity, and manage and screen for comorbidities (Luqmani et al., 2009).

2.9.1 Pharmacological treatment

There are many different types of drugs used in treatment of RA disease: Non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying antirheumatic drugs (DMARDs), glucocorticoids, immunosuppressant biologic modifier agents (Akil & Amos, 1995b; O'Dell, 2004; Oliver & Clair, 2008). The main goal of

pharmacological treatment is to reinforce the overall main aim as outlined by the BSR. The decision of choosing the appropriate treatment intervention is important in preventing further damage to the affected joints or irreversible disability, and to preserve the body from permanent deformity.

2.9.1.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are a first line of treatment and are commonly used in the symptomatic treatment of many rheumatic diseases and other associated medical conditions (Akil & Amos, 1995b; Oliver & Clair, 2008). NSAIDs reduce swelling and pain in RA patients. These drugs are divided into two groups:

A) Non-selective NSAIDs, such as naproxen, ketoprofen, ibuprofen, diclofenac, piroxicam and indomethacin. These drugs inhibit both cyclooxygenase-1(COX-1) and cyclooxygenase-2 (COX-2), which is when the central enzyme is involved in synthesis of prostaglandins and related compounds (Hilliquin & Menkes, 1994; Oliver & Clair, 2008; Temprano & Smith, 2011). This group negatively triggers gastrointestinal irritation and precipitates asthma and fluid retention, due to decreased kidney function.

B) COX-2 selective inhibitor (COX-1 sparing agents) such as nemisulide, meloxicam, rofecoxib, valdecoxib. This type has a much superior gastrointestinal tolerance, but gives a considerable risk of cardiovascular problems, minimum or no effect on platelets, and no susceptibility to produce asthma (Firestein et al., 2006; Hilliquin & Menkes, 1994; Oliver & Clair, 2008).

All NSAIDs are analgesic, antipyretic and anti-inflammatory to relieve pain, reduce fever and eliminate inflammation. They have a rapid inhibitory result on

exacerbations of inflammation like pain and MS; unfortunately, this group has no inhibitory effect on the progression of RA and controls the symptoms only, without retarding the disease progression. A treatment strategy depends on the patient's response (Breedveld & Kalden, 2004; Oliver & Clair, 2008). A patient's response is variable and while it may necessitate trying several NSAIDs, the simultaneous combination of two NSAIDs should be avoided (Breedveld & Kalden, 2004; Oliver & Clair, 2008). Before assessing the treatment's efficacy to control pain, it should be used at full dosage continuously for at least two to four weeks, in order to maximise the anti-inflammatory effect (Oliver & Clair, 2008).

2.9.1.2 Disease modifying anti-rheumatic drugs (DMARDs)

DMARDs are one of the potent anti-inflammatory drugs that have a significant role in altering disease progression. They can be called slow acting anti-rheumatic drugs (SAARDs) or second-line agents (SLAs) (O'Dell, 2004; Oliver & Clair, 2008; Saag et al., 2008). DMARDs can significantly modify or control the disease through reduction of inflammation, lessening damage and maintaining joint function (Akil & Amos, 1995b; Oliver & Clair, 2008; Temprano & Smith, 2011). With different sites of action, most DMARDs' the mode of action of remains unclear and controversial but overall it is difficult to explain the multiple pathogenesis theories (Firestein et al., 2006; Oliver & Clair, 2008).

It has been proven and recommended that early initiation of DMARDs should be prescribed in order to induce more remissions and retard disease progression (Luqmani et al., 2009; Oliver & Clair, 2008; Temprano & Smith, 2011). There is good evidence that joint inflammation is controlled by DMARDs, and that

withdrawal of the drug leads to exacerbation of inflammation (Breedveld & Kalden, 2004; Saag et al., 2008; Shipley et al., 2005). Methotrexate (MTX), Sulphasalazine, leflunamide, and cyclosporine have been shown to reduce the rate of progressive joint damage (Breedveld & Kalden, 2004; Shipley et al., 2005). MTX is one of the most common DMARDs used because of its recognised clinical benefits, effectual combination with other DMARDs and its well-understood, long-term efficacy and toxicity profile (Oliver & Clair, 2008; Temprano & Smith, 2011). The mode of action of DMARDs is delayed a few months after use, and this gap can be covered by low-dose C/S, which provide rapid control of the signs and symptoms and thus act as bridge therapy (Oliver & Clair, 2008; Smolen et al., 2010).

The ultimate goal of drug therapy is to achieve remission; if the single drug of DMARDs does not achieve this goal, then combination of two or three drugs may be more effective than MTX alone (O'Dell et al., 1996; Oliver & Clair, 2008; Saag et al., 2008; Smolen et al., 2010). In a study by Boers et al. (1997), the use of sulphasalazine (2g/day), prednisolone (60 mg/day), and MTX (7.5 mg/week) was investigated in 155 early RA patients for 52 weeks compared to those receiving Sulphasalazine alone (Boers et al., 1997). The results showed that joint damage was significantly less in the combination regimen. DMARDs, in spite of their therapeutic effectiveness, cause adverse effects; some are temporary while others might be fatal. Although the incidence of fatalities is unknown, most of the side effects are related to toxicity or bone marrow suppression (Breedveld & Kalden, 2004; Dixon & Daniel, 1993).

It is logical to start treatment with drugs that have the least toxicity, for instance: hydroxychloroquine and sulphasalazine. DMARDs are crucial to the control of disease activity and consequential joint damage. They offer outstanding disease control and deter permanent joint injury; therefore, combinations of DMARD regimens are recommended. If the onset of action is delayed or there are adverse toxic reactions to DMARDs, the administration of the third-line agent, C/S, could be substituted.

2.9.1.3 Corticosteroids (C/S)

C/S, steroids and glucocorticoids, play a vital role in medicine and particularly in rheumatology (Oliver & Clair, 2008; Saag et al., 2005). The actions of C/S are strongly anti-inflammatory and immunosuppressive, reducing activation, proliferation, differentiation and survival of a variety of inflammatory cells such as macrophages and T-lymphocytes (Firestein et al., 2006; Oliver & Clair, 2008). However, they are powerful disease-controlling drugs with inevitable side effects; therefore, they should be avoided in the long term (Oliver & Clair, 2008; Shipley et al., 2005).

Corticosteroids are used in the following ways:

- Started and maintained in low dose (5-10 mg) as additional therapy to improve known symptoms of RA (Oliver & Clair, 2008; Saag et al., 2005). Some centres use early intensive short-term regimens (Shipley et al., 2005). Because of side effects such as osteoporosis, they should not be used for long-term therapy (Saag et al., 2005).
- As a bridge therapy to relieve the symptoms while waiting for the therapeutic effect of DMARDs (Oliver & Clair, 2008).

- Sometimes steroids are prescribed in serious systemic active RA such as vasculitis and serositis in suitable infusion dose therapy as pulse dose to induce remission and dramatic response (Hilliquin & Menkes, 1994; Kadioglu & Sheldon, 1998; Oliver & Clair, 2008).
- Intra-articular injections are administered in acute inflammatory arthritis to improve function, mainly in weight-bearing joints with effusion. Intra-articular injection is indicated in tenosynovitis, bursitis, and carpal tunnel syndrome (Hilliquin & Menkes, 1994; Oliver & Clair, 2008).
- Steroids have many adverse side effects, such as osteonecrosis, osteoporosis, hyperglycaemia, glaucoma, cataract, impaired wound healing, truncal obesity, flushing face, amenorrhea, myopathy, peptic ulcer, hypertension (HT), skin thinning and psychosis; some of these adverse reactions might be temporary, while others could be permanent (Hilliquin & Menkes, 1994; Oliver & Clair, 2008). The adverse publicity about the potential side effects of steroids has meant that their use is now controversial (Myasoedova et al., 2011; Shipley et al., 2005). Another main problem associated with steroids is withdrawal symptoms in those patients with long-term usage, which occurs due to potential side effects (Hilliquin & Menkes, 1994; Oliver & Clair, 2008; Shipley et al., 2005). To avoid flare up of disease activity, tapering of the dosage must be done carefully depending on duration of treatment, severity and clinical response.

C/S are valuable mainly in active inflammatory diseases with reasonably scheduled dose either alone or in combination with NSAIDs and DMARDs as

bridge, additive or pulse therapy. Moreover, careful assessment of the patient's history as well as a full examination is recommended if the patient complains of other chronic systemic diseases. This is especially important among elderly people who already might have a compromised immune system. It is necessary to advise those patients on long-term steroid therapy to be aware of the dangers of falling over and/or mal-nourishment due to the fact that steroids can cause decreased bone density.

2.9.1.4 Biologic response modifier

This group of drugs was designed in the past decade and has revolutionised the treatment of RA. These drugs can reduce inflammation without causing permanent joint damage and can increase damaged joint function (Gordon & Hastings, 2004; Singh et al., 2009; Weaver, 2004). They work as modifiers in pathogenesis of RA, principally in binding molecules onto the cells of the immune system (Gordon & Hastings, 2004; Oliver & Clair, 2008). The molecules of immune cells cause inflammation followed by joint destruction (Gordon & Hastings, 2004; Shipley et al., 2005; Weaver, 2004). The evidence from use of biologic drugs suggests that a new direction in RA therapy has begun, wherein it depends on immune-regulatory interference (Luqmani et al., 2009).

This group is characterised by a rapid mode of action, within two weeks for some medications, and four to six weeks for others. However, most anti-TNF drugs require a minimum of three months' treatment before effectiveness can be determined, and several need six months of therapy to show significant changes in RA symptoms (Gordon & Hastings, 2004; Oliver & Clair, 2008; Saag et al., 2008). These drugs are very expensive compared to DMARDs or C/S (Oliver &

Clair, 2008; Weaver, 2004). The guideline from the British Society of Rheumatology (BSR) UK recommend that biological therapy should be reserved for patients with active disease and who have not responded to at least two DMARDs, including MTX, for a minimum of two months (Ledingham & Deighton, 2005; Luqmani et al., 2009). Moreover, the contra-indications and side effects of these drugs should be highlighted (Singh et al., 2012).

Recently, the ACR has updated the recommendation for the use of DMARDs and Biologic agents in terms of:

- Indications of both DMARDs and biologics;
- Switching between drugs (Singh et al., 2012);
- Screening for tuberculosis (TB) reactivation in patients starting or currently receiving biologic agents (Singh et al., 2012);
- Initiation of biologic agents in high-risk cases with hepatitis, congestive heart failure and malignancy (Singh et al., 2012);
- Vaccination for those patients starting or currently receiving DMARDs or biologic agents (Singh et al., 2012).

The main side effects of biologic drugs are upper respiratory tract infections and erythematous skin reaction at the injection site, which will disappear after a few days (Weaver, 2004). Symptomatic relief of pain and swelling can be achieved by using NSAIDs. Early treatment with DMARDs and introducing biologics are the most important factors to be considered (Weaver, 2004). Sometimes effective control of disease activity will require more than one medication (Weaver, 2004).

2.9.2 Non-pharmacological treatment

Varieties of non-pharmacological treatment approaches to manage the symptoms of RA and improve overall wellbeing for RA patients have been investigated (Schur & Moreland, 2011). It has been recommended that some important factors should take into account the rehabilitation of people with rheumatic diseases, such as the restriction of mobility and activity (Schur & Moreland, 2011). Rehabilitation is concerned with managing the consequences of disease (Vlieland & Thea, 2003). As no drug therapies at present lead to long-term remission of RA, patients will continue to suffer physical, psychological, functional and social disease consequences, the severity/impact of RA consequences could be reduced by rehabilitation (Vlieland & Thea, 2003).

The major components of rehabilitation therapy include education and counselling, relative rest, pain-relieving modalities, nutrition, adaptive devices and exercise (Beardmore, 2008; Schur & Moreland, 2011). The main objectives of rehabilitation are to maintain or improve joint mobility, increase muscle strength to prevent further joint damage and achieve maximum physical function (Beardmore, 2008; Schur & Moreland, 2011).

2.9.2.1 Education and counselling

Education and counselling are vital in order for RA patients and their carers to understand the nature, onset, and complications of the disease (Beardmore, 2008; Schur & Moreland, 2011). There is a need to plan long-term treatment in order to appraise and assess alternative treatment options and identify reasonable expectations (Beardmore, 2008; Schur & Moreland, 2011). An understanding of the disease helps patients and carers to cope psychologically with the impact of

the disease's symptoms, such as pain and disability, and minimises visits to physicians (Temprano & Smith, 2011). Education and self-management may be the most cost-effective intervention for RA (Temprano & Smith, 2011).

2.9.2.2 Physical modalities

2.9.2.2.1 *Bed rest*

An inflamed joint needs to be rested using either splints or taking bed rest to avoid further destruction and deformity (Hurley et al., 2002; Schur & Moreland, 2011). However, because the most common symptom of RA is fatigue (Schur & Moreland, 2011), long-term periods of rest should be avoided, and instead short-term periods of rest should be alternated with physical activity in order to prevent muscle atrophy (Oliver & Clair, 2008; Schur & Moreland, 2011). Rest and splinting for fingers and wrists, which work to reduce joint swelling and pain, are commonly used during active disease (Beardmore, 2008; Schur & Moreland, 2011). Tradition recommends admission to hospital for prolonged bed rest and immobilisation to control disease activity (Mills et al., 1971; Ropes, 1961). However, muscle atrophy often accompanies RA and is exacerbated by prolonged bed rest, immobilisation, splints and medications (Temprano & Smith, 2011).

It is best to rest the joints that are inflamed in RA patients during flare-ups (worsening of joint inflammation) (Scott & Wolman, 1992). This may be accomplished by the temporary use of adaptive devices or joint splints (Hurley et al., 2002; Schur & Moreland, 2011). When joint inflammation is decreased, guided exercise programmes are necessary to maintain flexibility of the joints and to strengthen the muscles that surround the joints. Range of motion exercises

should be carried out regularly in order to maintain joint mobility (Hurkmans et al., 2009; Hurley et al., 2002; Vliet Vlieland & Van den Ende, 2011). However, Patients with RA should not stay in bed for more than 48 hours without having a medical consultation (Hurkmans et al., 2009; Hurley et al., 2002; Scott & Wolman, 1992; Vliet Vlieland & Van den Ende, 2011).

2.9.2.2.2 Exercise therapy

Exercise is the cornerstone of the non-pharmacological treatment of RA; its main function is to improve muscle strength, endurance and GWB (Hurkmans et al., 2009; Vliet Vlieland & Van den Ende, 2011). Terms such as physical activity and exercise can describe different concepts (Caspersen et al., 1985). These terms are sometimes used interchangeably and they are often difficult to distinguish between (Caspersen et al., 1985). In this thesis, physical activity is referred to in the context of: any body movement generated by skeletal muscles, resulting in energy expenditure, such as activities of daily life in terms of occupational, sport conditioning and household (Caspersen et al., 1985). Exercise is referred to as a division of physical activity that is planned, structured, and repetitive, and has a target for the improvement or maintenance of physical fitness (Caspersen et al., 1985). Patients with RA experience severe pain and stiffness because of joint inflammation, the consequences of which may lead to loss of joint motion, loss of muscle strength, muscle atrophy and contractures. This, in turn, leads to decreased joint stability and further increased fatigue (Hurley et al., 2002; Schur & Moreland, 2011).

In RA patients, one of the most important points is to strike a balance between rest and exercise, which can be tailored and modified depending on the clinical condition (Frank, 2010). A variety of exercises may be considered as beneficial to RA patients in helping improve range of movement, strength and endurance. These may include isometric, isotonic, isokinetic, walking, swimming and cycling (Beardmore, 2008; Hurley et al., 2002; Schur & Moreland, 2011). One question that needs to be asked, however, is whether or not some interventions that are aimed principally at improving other variables also reduce fatigue. For instance, pharmacological interventions were prescribed to reduce inflammation, exercise interventions administered to improve physical activity and psychological behavioural therapy indicated to improve psychological distress and all these treatment modalities might reduce fatigue in RA (Hewlett et al., 2011; Hewlett et al., 2008).

Recent evidence suggests that exercise has a positive effect on joints, and has no harmful effect on the patient in relation to disease activity or pain. A systematic review by Van den Ende et al. (2007) emphasised that there were no detrimental effects on RA patients of dynamic exercise therapy, but rather that there was a positive effect from exercise.

Hydrotherapy

Hydrotherapy is a combination of therapeutic exercises and immersion in warm water (Beardmore, 2008). ‘Hydrotherapy’, otherwise known as ‘aquatic exercise’ or ‘aquatic therapy’, is defined as the controlled exercise in warm water using the buoyancy, assistance and resistance of warm water to relieve pain, induce muscle

relaxation and promote more effective exercise (Ahern et al., 1995). It is now called 'aquatic physiotherapy' and is highly valued as an excellent exercise for patients with arthritis (HyDAT Team, 2009).

The main aim of hydrotherapy is to relieve pain, improve joint motion, promote feelings of comfort, and consequently improve function and QoL (Ahern et al., 1995; Foley et al., 2003). Hydrotherapy is advocated as a safe and efficient medium for achieving exercise-related goals, and it is commonly used for patients with rheumatic disease (Beardmore, 2008; Rintala et al., 1996). The difference between aquatic exercise and exercise on land is that floating in water has been found useful in relaxing the muscles. Some exercises are made easier due to the buoyancy of the water; some are made more difficult due to the resistance provided by the water (Foley et al., 2003; Rintala et al., 1996).

Immersion in the thermo-neutral water temperature has a soothing effect and plays an important role providing an optimum environment for exercise (Eversden et al., 2007; Verhagen et al., 2008). Water is an appropriate environment for treating RA patients because it helps relax tense muscles and increases blood flow to the tissues (Bood et al., 2007; Kjellgren et al., 2001; Melzack & Wall, 1967). It also has a sedative effect on nerve endings, and therefore reduces pain and discomfort (Bood et al., 2007; Kjellgren et al., 2001; Melzack & Wall, 1967). It is suggested that this form of treatment helps RA patients manage their disease independently for longer, preventing or reducing hospital admissions and enabling a speedy return to occupations, which therefore reduces the cost impact on employers and society.

2.9.2.2.3 Heat and cold therapy

The use of hot and cold water has been commonly indicated for centuries in most musculoskeletal illnesses and impairments, especially in acute injury (Beardmore, 2008; Hurley et al., 2002). Heat and cold are used to reduce pain and decrease stiffness in many rheumatic and musculoskeletal conditions such as OA (Hurley et al., 2002). This treatment is easy to use, is low-cost, and can be used in the home, outpatient clinic and private office (Beardmore, 2008). A Cochrane review in 2002 by Robinson et al. supported also by Welch et al. (2011), found that heat and cold had no effects on the objective measures of disease activity, and no harmful effects of thermotherapy were reported (Robinson et al., 2002; Welch et al., 2011).

Heat therapy can be applied as hot packs, water baths, paraffin wax, or thermal packs. Water baths or Whirlpools can be combined with active or passive motion of exercises to increase the range of joint movement (Beardmore, 2008; Hurley et al., 2002; Welch et al., 2011). Thermal packs contain chemical agents, which produce heat through the occurrence of an exothermic reaction upon activation (Beardmore, 2008; Hurley et al., 2002; Welch et al., 2011). Heat therapy is contraindicated in the absence of normal sensation or impairment or diminished blood supply, mainly in people with diabetes (Beardmore, 2008; Hurley et al., 2002; Welch et al., 2011).

Application of cold is used for immediate care after musculoskeletal injury because it causes vasospasm and is associated with reduction in tissue inflammation and oedema; therefore, it reduces pain, muscle spasm and

circulation (Beardmore, 2008). This type of treatment should be applied locally for up to 30 minutes, but deep cooling is reliant on application time and soft tissue depth (Beardmore, 2008).

2.9.2.2.4 Electrotherapy

There are many types of electrotherapy such as transcutaneous electrical nerve stimulation (TENS), interferential and laser, all of which may be used to relieve pain in non-inflammatory chronic conditions such as back pain, knee pain, chronic shoulder pain or other joint pain (Beardmore, 2008). The evidence for effectiveness of these treatments in RA is uncertain and poorly evaluated (Beardmore, 2008; Hurley et al., 2002; Minor & Sanford, 1993).

2.9.2.2.5 Joint protection, the provision of adaptive devices and walking aids

Walking aids and adaptive devices are frequently prescribed to RA patients (De Boer et al., 2009) with the aim of improving or maintaining functional ability and independence, relieve pain and improve mobility by reducing lower-limb loading (De Boer et al., 2009; Hurley et al., 2002).

Gutter frames and fisher sticks, are effective at redistributing the load onto the small joints of the upper limbs (Hurley et al., 2002). There is a strong relationship between the usage of adaptive devices with patients of an older age, more severe disease and more acute disability (De Boer et al., 2009), although these aids may enhance the negative perceptions of patients' feeling of being old and infirm (Hurley et al., 2002). Moreover, a number of factors have not been taken into account – factors which are more likely to be relevant for the actual usage of adaptive devices, such as the process of prescription and provision and the

patient's evaluation of the design and comfort of adaptive devices (De Boer et al., 2009).

2.9.2.2.6 Nutrition and dietary therapy

A nutritionist is another professional needed for the holistic care of all RA patients. This is due to the fact that people with RA have many challenges related to appetite loss, adequate amount of calories and nutrients, risk factors for coronary disease, and the need to reduce stress on inflamed joints in overweight and obese patients (Ariza-Ariza et al., 1998; James & Cleland, 1997; Kremer, 2000).

2.10 Overall summary

This chapter has discussed the background of RA, in terms of definition, epidemiology, clinical features and pathophysiology. Furthermore, this chapter provided an overview of non-pharmacological and pharmacological therapy. It is reported that RA affects approximately 1% of all ethnic groups in the UK (Symmons et al., 2002). Although, RA can present at any age, it is more common in females and classically presents in middle age. The cause of RA is unknown; however, 30% of its aetiology is related to genetic factors.

The treatment goal in RA patients is to control synovitis early and to prevent joint damage, disability and complications. Physiotherapy or rehabilitation services play a major role in the management of RA by relieving pain and stiffness and providing patient education and advice. While exercise is the cornerstone of RA rehabilitation, many other modalities such as electrotherapy and thermotherapy are also commonly used.

The next chapter focuses upon hydrotherapy in terms of definition, physical properties, history, indications, contra-indications, and applications.

CHAPTER THREE: HYDROTHERAPY DETAILS

3.1 Introduction

The term hydrotherapy was derived from the Greek, hydro that refers to (water) and therapeia, which refers to (healing) (Duffield, 1976). Hydrotherapy treatment is regarded as one of the most ancient remedies in the world, and it is accepted that its use is as old as the history of humanity (Bender et al., 2005; Jackson, 1990; Sinclair, 2007). The use of hydrotherapy dates back several centuries before other treatments indicated in physical medicine (Bender et al., 2005; Schrepfer, 2002). The use of aquatic therapy to facilitate exercise began to grow in popularity near the end of the 19th, century, mainly in Europe but also followed by the USA (Schrepfer, 2002).

Aquatic exercise has been successfully indicated for a wide variety of rehabilitation programmes including paediatric, rheumatic, orthopaedics, cardiopulmonary and neurological patients (Geytenbeek, 2008; Hall et al., 2008; Schrepfer, 2002). In rheumatic and orthopaedic conditions, the use of hydrotherapy as a treatment is widely accepted and recognised, even though there is little objective evaluation of its therapeutic efficacy (Becker, 2009; Geytenbeek, 2008; Schrepfer, 2002). To date, there is limited published data on the effectiveness of hydrotherapy as a treatment modality for RA (Geytenbeek, 2008; Hall et al., 2008; Hall et al., 1996). It also appears that there is conflicting evidence regarding hydrotherapy experiences in patients with RA (Bilberg et al., 2005; Hall et al., 1996; Rintala et al., 1996; Stenström et al., 1991). The use of

hydrotherapy in RA was monitored to assess its ability to enhance performance and wellbeing (Eversden et al., 2007). Hydrotherapy is regarded anecdotally as one of the most effective treatments for long-term management of symptoms of rheumatological disorders (Bilberg et al., 2005; Hall et al., 1996; Rintala et al., 1996; Stenström et al., 1991).

Objective

The objective of this chapter is to review the water-based definitions and historical background of hydrotherapy and discuss issues related to the principles, physical properties, indications and contra-indications of hydrotherapy.

Definitions

Numerous terms or definitions related to water-based treatments have been found in the literature such as:

Whirlpool: Submersion of the external body in forced pressurised water (Geytenbeek, 2008).

Spa therapy: A specific thermal water spring that was found to have therapeutic qualities was discovered in the sixteenth century in a Belgian village named Spa. (Sukenik et al., 1999). In this type of therapy, the patients receive not only thermal mineral water but also other modalities such as massage, electrotherapy, and exercise (Bender et al., 2005).

Balneotherapy: This involves exercises in naturally mineralised water by the use of baths (hot or cold springs or naturally occurring waters) and other natural remedies (including mud) for healing (Bender et al., 2005; March & Stenmark, 2001; Strauss-Blasche et al., 2002). This type of therapy includes minerals and elements such as sodium, potassium, calcium, iodine and magnesium (Bender et

al., 2005). Moreover, it includes the Anion of SO_4^{2-} , Cl^- , and HCO_3^- , the waters must be bacteriologically pure (Bender et al., 2005).

Thalassotherapy: Originally derived from the Greek word *thalassa*, meaning "sea" (Charlier & Chaineux, 2009; de Andrade et al., 2008), this term refers to seawater therapy and originated from the French Sea and Health Federation in 1986 (Charlier & Chaineux, 2009; de Andrade et al., 2008). Under the supervision of medical staff, thalassotherapy is a combination therapy with a curative and preventive goal that utilises the benefits of the marine environment, such as the marine climate, seawater, mud, sand, seaweed and other substances derived from the sea, (Charlier & Chaineux, 2009; de Andrade et al., 2008).

Kneipp therapy This term was created relatively recently by the Bavarian almoner and Dominican priest, Sebastian Kneipp (1821-1897), who used it to refer to alternate warm- and cold-water therapy (Goedsche et al., 2007; Koeppen & Kostka, 1960; Schencking et al., 2009). Also known as 'Kneipping' or 'The Kneipp Cure' it was first used by German physicians (Koeppen & Kostka, 1959). It is an application of cold and warm water of varying degrees of temperature and pressure by showers and towels (Koeppen & Kostka, 1959; Schencking et al., 2009).

Hydrokinesiotherapy: Patients perform exercises in warm seawater by taking advantage of the buoyancy and the therapeutic capacities of seawater; this therapy has been suggested for people with musculoskeletal problems (Balogova et al., 2003; Geytenbeek, 2008).

3.2 Historical background

The application of water as a healing therapy dates back several centuries (Schrepfer, 2002; Roberts, 1981; Sinclair, 2007). Historical background study of hydrotherapy (curative and recreational) is well documented and has been intensively reviewed by many authors such as Jackson (1990) and Campion (1997). A number of reviews of the history of hydrotherapy have been published (Campion, 1997; Jackson, 1990; Price, 1981; Wyman & Glazer, 1944).

The history of hydrotherapy in physical medicine goes back many thousands of years with records dating back to 2,400 BC (Jackson, 1990; Karel & Tolliver, 2003). It has been suggested that Egyptians, Assyrians and Mohammedans used mineral waters for curative purposes, and proto-Indian culture created and manufactured hygienic installation (Campion, 1997; Sinclair, 2007). A great upsurge in the use of water treatment was revealed in the first century BC and in 1500 BC, and there is evidence showing that the Hindus used water to treat fevers (Campion, 1997; Jackson, 1990).

Jackson (1990) gives examples of the use of thermal baths in treatment of many conditions such as soothing chest and back pain, treating pneumonia to improve respiration, reducing fatigue, relaxing joints and relieving headaches. Moreover, herbal oil extract was added to warm baths and the use of aromatic vapour baths was advised in cases of 'female disorders' (Jackson, 1990). The Greeks also used hydrotherapy as part of remedial therapy, and were among the first to be aware of the benefits of physical and mental well-being in general. They developed

hydrotherapy centres close to springs and rivers using them for bathing and recreation (Campion, 1997; Jackson, 1990; Sinclair, 2007).

In 1924, Franklin Roosevelt visited the warm springs to receive aquatic therapy (Becker, 2009; Campion, 1997). During the 1930s, professional journals published many papers on pool and spa therapy because of the Presidential visit (Becker, 2009). In 1935, at hot springs in Arkansas City, Smith designed a swimming pool with warm water for patients with chronic atrophic arthritis for special underwater exercises and pool therapy (Becker, 2009).

One of the most important events that resulted from World War II, was the knowledge about maintaining the fitness of the army through exercising in water (Ahern et al., 1995; Campion, 1997; Rorke, 1996). This new knowledge also further fuelled the current upsurge of the use of hydrotherapy as a means of rehabilitation for a wide range of conditions (Ahern et al., 1995; Campion, 1997).

3.3 Principles of hydrotherapy

It is advisable for all practitioners to understand the physical principles of hydrotherapy and characteristics of water in order to make the medical use more rational and efficient (Becker, 2009; Salzman, 2003). Most movement in water is regarded as a learned skill that takes time to develop. However, movement response and activity in water is subtle and needs to be developed and closely monitored (Campion, 1997; Prins, 2009). Thus, the person who is unfamiliar with hydrotherapy can be expected to be more apprehensive than someone who has previous aquatic experience. This experience can be a barrier to recovery because

of the risk of counterproductive movements, utilisation of previous movement patterns that may exacerbate symptoms and prolong the recovery period (Edl et al., 2004; Prins, 2009).

In water two forces apply, one for gravity (down thrust) and the other for buoyancy (up thrust), which concurrently act upon the body (Edl et al., 2004; Prins, 2009). Thus, it provides the body with an exercise medium and experience that are not available with land-based treatments (Salzman, 2003). Water permits movement and activities for non-weight bearing joints to be activated (Edl et al., 2004; Prins, 2009). The hydrodynamic principles are responsible for the development of hydrotherapy practice in physiotherapy (Becker, 2009; Schrepfer, 2002). This includes buoyancy and hydrostatic pressure, depending on Archimedes' principle and Pascal's Law (Campion, 1997; Prins, 2009; Salzman, 2003; Schrepfer, 2002).

Archimedes' principle states that (Campion, 1997, pp.14)

"When a body is immersed in a fluid, it experiences a buoyant force equal to the weight of fluid which the body has displaced."

In other words, according to Archimedes, if the upward thrust is greater than or equal to the weight of the immersed body, the body will float; if not, the body will sink. Anybody wholly or partially submerged in a fluid experiences an up-thrust force equal to the weight of the fluid displaced by the object (Salzman, 2003). Some exercises in water are made easier by the presence of the water, while others, such as walking, are more difficult according to Archimedes' law

(Campion, 1997; Salzman, 2003). When discussing hydrostatic pressure, Schrepfer (2002, pp.275), who was familiar with Pascal's Law, states that:

"The pressure exerted by fluid on an immersed object is equal on all surfaces of the object."

3.4 Mechanism of action

Many factors, such as buoyancy, immersion pressure, resistance and temperature, play an important role in the mechanism of hydrotherapy (Bender et al., 2005; Hall et al., 2008; Melzack & Wall, 1967). Buoyancy effect eliminates or counteracts the effect of gravity and allows for freedom and comfort of movement of joints and muscles, resulting in an apparent reduction in weight-bearing load through the spine and lower extremities (Campion, 1997; Edl et al., 2004; Salzman, 2003).

According to the pain gate theory in hydrotherapy, pain relief may be due to the water pressure and temperature. The warmth of the water has a sedative effect on nerve endings and therefore reduces pain and discomfort (Bender et al., 2005; Kjellgren et al., 2001; Melzack & Wall, 1967). Moreover, warm water relaxes tense muscles and increases blood flow to the tissues, facilitating muscle relaxation (Bender et al., 2005; Hall et al., 2008; Kjellgren et al., 2001; Lange et al., 2006). Water immersion induces an increase in methionine-enkephalin plasma levels, which is associated with a significant fall in mean arterial pressure and heart rate. Conversely, the effect of water pressure on skin suppresses plasma β -endorphin, corticotrophin, and prolactin levels (Coruzzi et al., 1988). This pressure also has an effect on the light and deep touch receptors in nerve endings,

helping to dissipate the pain-carrying fibres from passing their 'painful' messages to the brain (Bender et al., 2005; Yamazaki et al., 2000).

Other mechanisms are based around the effects of hydrostatic pressure, which because of its effect on the cardiovascular system, may relieve pain by reducing peripheral oedema and offset the pooling of blood in the lower extremities, offering graduated pressure at a greater depth (Becker, 2009; Butler, 2005; Campion, 1997; Salzman, 2003).

3.5 The physical properties of water

Two important physical properties of water, buoyancy and viscosity are key elements in designing effective aquatic exercises. It is due to hydrodynamics principles that immersion in water has biological effects that are recommended for medical applications (Bender et al., 2005; Campion, 1997; Salzman, 2003; Schrepfer, 2002). The physical properties of water that have the potential of physiological changes are relative water density, hydrostatic pressure, buoyancy (resilience) and thermodynamics (Becker, 2009; Campion, 1997; Edl et al., 2004; Schrepfer, 2002).

3.5.1 Relative density

The relative density of water is defined as the ratio of the density of a substance to the density of water, based on Archimedes' principle (Campion, 1997; Edl et al., 2004). Therefore, any object with less than a density of one will float in water, and any object with a density greater than 1.0 will sink (Campion, 1997; Edl et al., 2004; Schrepfer, 2002).

The relative density of the human body varies with age and is dependent upon gender (Becker, 2009; Campion, 1997). Men, on average, have higher density than women due to bone density and lower body fat. In young children, relative density is about 0.86 (Becker, 2009; Campion, 1997; Edl et al., 2004). Density of the mass of lean body, such as bone, muscle, connective tissue and organs is about 1.1, while the mass of body fat and excess fat has a density of approximately 0.9 (Bloomfield & Fitch, 1995; Edl et al., 2004). According to Archimedes' theory of principle, the human body is able to displace a volume of water greater than the weight of the body because the water pushes the body upward by a force equivalent to the displaced volume of water (Becker, 2009; Edl et al., 2004).

3.5.2 Hydrostatic pressure

By definition, hydrostatic pressure is the pressure that is exerted equally on any immersed objects depending on Pascal's law, at any level in a horizontal direction at a constant depth (Campion, 1997; Edl et al., 2004; Schrepfer, 2002). Thus, fluid pressure is exerted on all surfaces of an immobile immersed body at a certain depth (Campion, 1997; Edl et al., 2004). The main clinical significance of this pressure force is to eliminate oedema in the injured body part (Becker, 2009; Butler, 2005; Campion, 1997).

There is a positive correlation between density of water and depth of immersion; if the depth of the immersion increases, the pressure force is increased, and therefore the hydrostatic pressure also increases (Becker, 2009; Edl et al., 2004; Schrepfer, 2002). When the body is immersed in the water, the pressure it exerts will increase the distal venous pressure (blood is displaced ascending through one-

way circulatory system and the shift of blood to the thorax is increased), which assists in the venous return and increases the preload of the heart because of central hypovolaemia with subsequent cardiovascular response (Becker, 2009; Edl et al., 2004; O'Hare et al., 1985; Salzman, 2003; Schrepfer, 2002; Weston et al., 1987). As a result, heart rate may slow leading to an increase in stroke volume and ejection fractions (Becker, 2009; Edl et al., 2004; O'Hare et al., 1985; Salzman, 2003; Schrepfer, 2002; Weston et al., 1987).

Additionally, this pressure will give increased pulmonary blood flow, centralised peripheral blood flow, and increased central blood volume and pressure, which leads to greater perfusion of coronary arteries and more efficient cardiopulmonary system during exercise (Becker, 2009; Edl et al., 2004; Salzman, 2003; Schrepfer, 2002).

Hydrostatic pressure also serves as a progressive resistive exercise program for respiration because it restricts chest wall expansion (Edl et al., 2004; Salzman, 2003). Blood displaces vertically, leads to increased right atrial pressure and pleural surface pressure, the chest wall compresses, and the diaphragm is displaced vertically. Finally, the relationship of depth to pressure means that performing exercises below the water's surface smooth's out jerky movements, increasing coordination (Becker, 2009; Campion, 1997; Schrepfer, 2002).

3.5.3 Buoyancy (resilience)

Buoyancy can be defined as the upward force exerted by a fluid acting in the opposite direction to the gravity force, or opposite to the weight of an object (Campion, 1997; Edl et al., 2004; Schrepfer, 2002). Thus, two opposing forces

affect a body in water: gravity acting through centre of gravity and buoyancy acting through the centre of buoyancy (Campion, 1997; Edl et al., 2004; Schrepfer, 2002). When both centres are not aligned perfectly a rotational force occurs which assists the flotation of the body (Campion, 1997; Edl et al., 2004; Schrepfer, 2002). The advantages derived from buoyancy can be used in rehabilitation programmes; when a person enters the water, there is an immediate reduction in the effect of gravity on the body so that the water can assist and support body movement on the water's surface (Becker, 2009). The degree of effort is determined by the size of the moving body or limb, coupled with the velocity of the movement (Prins, 2009; Becker & Cole, 1997; Schrepfer, 2002; Skinner & Thomson, 1983; Ruoti et al., 1997).

Buoyancy assists free movement with less risk of injury and enables the therapists to facilitate resistance exercises (Bruce & Cole, 2011; Eversden et al., 2007; Prins, 2009; Schrepfer, 2002). Buoyancy offers weightlessness and joint unloading; this promotes muscle relaxation and allows exercise against water resistance, permitting the performance of active motion and increasing active exercise, and can help to improve functional ability (Schrepfer, 2002).

When the body is gradually immersed, water is displaced, which creates the force of buoyancy to counterbalance gravity and support the body, therefore gradually relieving the load on weight-bearing joints (Becker, 2009). The human centre of buoyancy is in the mid-chest, while the human centre of gravity is located posteriorly at the level of second sacral vertebrae (Becker, 2009; Edl et al., 2004;

Schrepfer, 2002). The more of the body immersed in water, the less it weighs (Becker, 2009; Schrepfer, 2002).

People immersed up to the symphysis pubis have effectively offloaded 33-40% of the weight of their bodies, and when further immersed to the umbilicus it increases to approximately 50% (Becker, 2009). Xiphoid immersion offloads bodyweight by 60% or more based on whether the arms are overhead or at the trunk level (Becker, 2009).

Buoyancy has the potential of being a very useful therapeutic utility; for instance, painful hips or knees may not be mechanically stable under full-body loading. However, during water immersion, gravitational forces and buoyancy provide relative weightlessness, and joint unloading may be partial or complete so that only muscle torque forces act on the joint, allowing active assisted range-of-motion activities, gentle strength-building, and gait training (Becker, 2009; Schrepfer, 2002).

To sum up, the effect of gravity is decreased by the buoyancy effect of water, allowing for more freedom and comfort of movement of joints and muscles. Therefore, exercise in water produces less joint compression compared to land exercise, and provides a suitable environment for rheumatic patients to exercise aerobically.

3.5.4 Viscosity and turbulence

Viscosity describes resistance of the internal friction of fluid molecules during motion (Becker, 2009; Salzman, 2003; Schrepfer, 2002). On this basis, a limb

moving in water is subjected to the resistance effects of the fluid, and this resistance is correlated positively to the velocity of movement through liquid – this is also called the ‘drag force and turbulence’ (Becker, 2009; Schrepfer, 2002). Resistance of water viscosity is proportional to the velocity of movement in the water, and this resistance increases when more force is exerted against water (Becker, 2009). Thus during treatment in water when a person feels pain and stops movement, the force drops abruptly as water viscosity dampens movement almost immediately (Becker, 2009). It is important to remember that fluid is more viscous than air, and that as the temperature increases, the viscosity decreases because the molecules are increasingly separated by heat (Salzman, 2003).

Turbulence refers to the eddies that follow in the wake of an individual moving through a fluid (Becker, 2009; Salzman, 2003; Schrepfer, 2002). The production of turbulence is greatly dependent on body shape, and the degree of turbulence is dependent on the speed of the movement. If the movement is slow then the flow of the particles is almost parallel to the object and proceeds in a smooth, continuous curve (Campion, 1997; Schrepfer, 2002). Faster movement produces eddies, and the energy in these eddies is dissipated, reducing the pressure and increasing the drag on the body (Campion, 1997; Schrepfer, 2002).

Turbulence might be used in hydrotherapy to assist movement. Turbulence creates resistance with all active movements, and a long lever arm, for example, results in increased resistance (Schrepfer, 2002). Increasing the surface area of the object moving through water also increases resistance. Moreover, proximally stabilising an extremity during manual resistance exercises in the water requires the patient

to perform more work (Schrepfer, 2002). Conversely, distally stabilising an extremity requires the patient to perform less work. A significant clinical implication of this is the possibility that using the physical properties alone to create turbulence results in challenges to balance and coordination, problems that are experienced by RA patients.

3.5.5 Thermodynamics

It has been suggested that water conducts heat 25 times faster than air, and that it also retains heat 1000 times more than air (Becker, 2009; Edl et al., 2004; Schrepfer, 2002). The use of water for therapeutic purposes depends on its ability to retain heat and transfer heat energy (Becker, 2009). On this basis, the use of water in the treatment is very versatile because water keeps hot or cold and it surrounds the immersed body part (Becker, 2009). However, Table 3.1 (p.81) shows immersion temperatures for variable conditions. For instance, it is believed in some controversial studies that cool plunge tanks at a temperature of 10-15°C are sometimes used to treat overuse injury, to relieve severe muscle pain and speed recovery in athletic individuals (Becker, 2009).

Additionally, therapy pools with temperatures in the range of 27-29°C are used for less active patients such as those with multiple sclerosis or who require vigorous exercise (Becker, 2009). The most common type of therapy pool operates in range of 33.5°–35.5°C (Becker, 2009), they are commonly used in arthritis, spinal cord injury programme, Parkinson's programming, cardiac rehabilitation and other typical aquatic therapy indications. This temperature will produce therapeutic effects, and despite long sessions in the pool, sufficient

exercise will be achieved (Becker, 2009). Similarly, hot tubs are usually kept at 37.5°– 41°C, although 41°C is not recommended for active comfortable exercise, and may be used only for short periods of relaxation (maximum of 5-10 minutes). Use for long periods in cases of severe/recent bruising or circulation disorders should be avoided (Becker, 2009; Butler, 2005).

Table 3.1: Immersion temperatures (in °C) for rehabilitation issues. Reproduced with kind permission from Becker, 2009.

Suitable Activities	Cold (10-15)	Cool (26-29.5)	Neutral (33.5-5.5)	Warm (36-38.5)	Hot (37.5-41)
Post exertional recovery	X				
Contrast baths	X			X	X
Vigorous exercise		X			
Arthritis exercise			X		
Typical aquatic therapy			X		
Cardiac rehabilitation			X		
Multiple sclerosis exercise		X			
SCI programming			X		
Parkinson's programming			X		
Relaxation				X	X

3.6 Equipment for aquatic exercise

Many types of equipment exist for use in aquatic exercises. Floatation devices are sometimes employed to help the practitioner control and increase exercise intensity by using buoyant support to the body, for example to alter positioning or movement, challenge problems, assist balance and generate resistance to movement (Schrepfer, 2002). These devices have advantages in increasing the buoyancy effect to offer support, reduce compressive forces and lessen impact, increase resistance in movement away from the water's surface and assist movement to the water surface (Edl et al., 2004; Schrepfer, 2002). They are useful for support and balance and as resistance instrument (Edl et al., 2004; Schrepfer, 2002).

3.6.1 Collars, rings, belts, and vests

Inflatable cervical collars are used primarily to support the patient in a supine position and keep the head out of the water by providing buoyancy assistance (Edl et al., 2004; Schrepfer, 2002).



Figure 3.1: Cervical collars used in hydrotherapy (used with kind permission from Salford Royal Foundation Trust).

Variable sizes of floatation rings are used to support the extremities, wrists and ankles as part of patient positioning and relaxation (Edl et al., 2004; Schrepfer, 2002). These devices are also used for resistive movement exercises wherein the patient works against the buoyant forces. Moreover, there are many types of belt and vest that are used as buoyancy aids for extremities or the entire body in any position, whether vertical, prone or supine (Edl et al., 2004; Schrepfer, 2002). Floatation belts are available in different sizes and some have removable parts so that the amount of buoyancy can be changed. Sometimes bands can be attached to the belts.



Figure 3.2: Floatation rings used in hydrotherapy (used with kind permission from Salford Royal Foundation Trust).

3.6.2 Swim bars (buoyancy dumbbells)

These bars are available in both short and long lengths. They are indicated for use in supine or prone position for lower limb activities, and indicated for use in the upright position for upper limbs and trunk support (Edl et al., 2004; Schrepfer, 2002). Buoyancy dumbbells can be used for balance or proprioception in shallow water (Edl et al., 2004; Schrepfer, 2002). The long dumbbell can be used to strengthen the trunk in a seated or standing position in deep water (Edl et al., 2004; Schrepfer, 2002).



Figure 3.3: Swim bars used in hydrotherapy (used with kind permission from Salford Royal Foundation Trust).

3.6.3 Gloves, hand paddles and hydro-tone balls

The main goal of applying webbed gloves or large paddles to the hands is to enhance motion resistance in the direction of upper extremity movements, because these devices do not work as buoyancy aids (Edl et al., 2004; Schrepfer, 2002). In addition, hydro-tone bells, which are large slotted plastic devices, are indicated to generate resistance and increase turbulence for upper limb movements (Edl et al., 2004; Schrepfer, 2002).



Figure 3.4: Gloves and paddles used in hydrotherapy (used with kind permission from Salford Royal Foundation Trust).

3.6.4 Fins and hydro-tone boots

This equipment is indicated to increase the surface area that's moving through the water (Edl et al., 2004; Schrepfer, 2002). Fins and boots are indicated for the lower limbs in order to increase resistance during movement (Edl et al., 2004; Schrepfer, 2002). Fins can be applied to strengthen the muscle around ankle, hip and knee joints, whereas boots are used mainly for deep water walking and running (Edl et al., 2004; Schrepfer, 2002).



Figure 3.5: Fins used in hydrotherapy (used with kind permission from Salford Royal Foundation Trust).

3.6.5 Kickboards and woggles

Variable types and styles are indicated for any exercise programme, mainly to provide buoyancy and create resistance in any position, whether supine or prone (Edl et al., 2004; Schrepfer, 2002). These also apply in deep water for help with

seating kneeling and balance problems (Edl et al., 2004; Schrepfer, 2002). Woggles or ‘noodles’ can be used for upper and lower extremities at the same time because they encircle the body (Edl et al., 2004).



Figure 3.6: Woggles and kickboards, used in hydrotherapy (used with kind permission from Salford Royal Foundation Trust).

3.7 Indication, contraindication and precaution

In general, facilitation of functional recovery is the main purpose of aquatic exercise, by offering an environment that enhances a patients and/or practitioners’ ability to perform various therapeutic interventions (Edl et al., 2004; Schrepfer, 2002). Indications for aquatic therapy include (Edl et al., 2004; Schrepfer, 2002):

- Facilitation of ROM exercise in cases of loss of joint mobility;
- Assistance with weight-bearing activities;
- Initiation of resistance training and muscle strengthening;
- Facilitation of cardiovascular exercise;
- Enhancement of patient relaxation;
- Enhancement of functional activity;
- Provision of three-dimensional access to the patient;
- Improvement of the delivery of manual techniques;
- Improvement of co-ordination or balance;

- Improvement of gait training;
- Relief from pain and lack of confidence;
- Minimisation of the risk of injury or recurrent injury after rehabilitation.

The aquatic exercise selected should be easily accessible and tolerated by most individuals. However, the practitioner working in this field should consider all aspects of immersion in terms of physiological, clinical and psychological that affects the selection of aquatic pools (Edl et al., 2004; Schrepfer, 2002). When assessing the value of hydrotherapy for individual patients, there are some important factors to consider. Therapists need to exercise caution when faced with some situations such as hydrophobia (fear of water), which can restrict the effectiveness of any immersion activity (Edl et al., 2004; Schrepfer, 2002).

Apprehensive patients often experience increased symptoms because of muscle guarding, stress response, and improper form with exercise (Edl et al., 2004; Egan, 1981; Schrepfer, 2002). Patients with neurological disorders such as confusion, disorientation and ataxia may struggle in controlling purposeful movements. Multiple sclerosis patients may experience fatigue and other detrimental effects with immersion in temperatures greater than 33°C because of heat intolerance (Ruoti et al., 1997; Schrepfer, 2002).

However, patients with multiple sclerosis are not precluded from hydrotherapy in lower temperatures (Roehrs & Karst, 2004). Other conditions that require close monitoring during immersion treatment, such as controlled epilepsy (seizure), haemophilia, behavioural problems, angina and abnormal blood pressure, require close monitoring (Edl et al., 2004; Schrepfer, 2002). Patients with small open

wounds and respiratory problems such as tracheotomies can be immersed with caution (Edl et al., 2004; Schrepfer, 2002). The following conditions are regarded as absolute contraindication for hydrotherapy. These are:

- Cardiac failure and unstable angina (Edl et al., 2004; Schrepfer, 2002).
- Open wound and infective skin conditions such as tinea pedis and ringworm (Cole & Becker, 2001; Edl et al., 2004; Schrepfer, 2002).
- Respiratory failure, active TB and episodes of status asthmaticus (Campion, 1997; Edl et al., 2004; Schrepfer, 2002).
- Danger of bleeding or haemorrhage (Edl et al., 2004; Schrepfer, 2002).
- Severe peripheral vascular disease (Edl et al., 2004; Schrepfer, 2002).
- Very low, high or uncontrolled blood pressure (Campion, 1997; Edl et al., 2004).
- Uncontrolled seizures (epilepsy) (Edl et al., 2004; Schrepfer, 2002).
- Colostomy (Edl et al., 2004; Schrepfer, 2002).

3.8 Hydrotherapy in rheumatic diseases

The suggested benefits of hydrotherapy in rheumatic disease are similar for all other conditions; these benefits which can be related particularly to the warmth of the water (which relieves pain and muscle spasm) and buoyancy (which relieves stress on weight bearing joints) (Bender et al., 2005; Eversden et al., 2007; Hall et al., 1996; Schrepfer, 2002). For most rheumatic conditions like RA, the goals of treating patients by hydrotherapy are as follows (Ahern et al., 1995; Geytenbeek, 2002; Hall et al., 1996):

- Alleviation of joint pain and relax muscle spasm;

- Recovery and restoration of muscle strength;
- Minimisation of deformity and improvement of range of joint motion;
- Stretching of contractures in order to prevent further contractures;
- Preservation of muscle power around unaffected joints;
- Promotion of relaxation and joint mobilisation;
- Enhancement of coordination and improve functional ability;
- Amelioration of morale.

3.9 Overall summary

This chapter has explained the central importance of hydrotherapy in the treatment of many conditions and diseases. It is the suggestion of this research study that hydrotherapy, balneotherapy, and spa resort treatment should be considered as separate entities, similar to the classification of any other categories such as simple NSAIDs (Bender et al., 2005). It is clear that immersing the body in water produces many physiologic effects, the benefits of which have been used for treatment purposes over centuries of medical therapy.

It is recommended that aquatic programmes should be designed for treating individuals to enable them achieve fitness and restore body function. Hydrotherapy has been proven to protect the health and prolong lives and has been shown to be a good all-round workout because it involves most muscles and joints for those with RA (Arthritis Research UK, 2011; Becker, 2009). The next chapter examines the effectiveness of hydrotherapy as a modality for RA in a systematic review.

CHAPTER FOUR: THE EFFECTIVENESS OF HYDROTHERAPY IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW

4.1 Introduction

Exercise is the cornerstone of the non-pharmacological treatment of RA, and it is recommended to improve function, muscle strength, and GWB; however, it cannot replace the pharmacological treatment (Hurkmans et al., 2009; Van den Ende et al., 2007; Vliet Vlieland & Van den Ende, 2011). Hydrotherapy is a safe and suitable treatment modality for achieving exercise-related goals, and it is sometimes used as part of rehabilitation intervention for patients with RA (Beardmore, 2008; Rintala et al., 1996).

Unblinded studies that examined the efficacy of hydrotherapy in patients with RA demonstrated a reduction in pain and an improvement in QoL, muscle strength, aerobic conditioning and physical functioning (Danneskiold-Samsøe et al., 1987; Hart et al., 1994; Minor et al., 1989). However, the generalisability of the findings were limited because of the small sample sizes and a lack of controlled intervention.

Aim

- To determine the effect of hydrotherapy in the management of patients with RA by conducting a systematic review.

To the knowledge of the present researcher, there has been no recent exclusive systematic review to examine the efficacy of hydrotherapy for patients with RA. The hypothesis of this research study is that hydrotherapy is far superior compared to other types of therapy – including ‘usual care’ – for improving QoL and physical activity in patients with RA. The aim of this review was to synthesise the available literature on the efficacy of hydrotherapy in the management of patients with RA.

4.2 Materials and methods

4.2.1 Identification and selection criteria

An electronic database search of Allied and Complementary Medicine (AMED), Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, Excerpta Medica Database (EMBASE), Medical Literature Analysis and Retrieval System Online (MEDLINE), ProQuest Research Library (ProQuest), PubMed Central (Pub-Med), Science Direct, and the Web of Science was conducted (1988 to September 2013). In order to standardise the patient sample included, the search was conducted from 1988 [which was the date of the publication of the ACR criteria for RA] to September 2013 (Arnett et al., 1988).

The search was limited to human adults (age >18 years) across all articles published in English. The keywords used were ‘rheumatoid arthritis’, ‘hydrotherapy’, ‘aquatic physiotherapy’, ‘aqua therapy’, and ‘water therapy’. Keyword combinations were ‘rheumatoid arthritis and hydrotherapy’, ‘rheumatoid arthritis and aquatic physiotherapy’, ‘rheumatoid arthritis and aqua therapy’, ‘rheumatoid arthritis and water therapy’. Studies that used the following keywords

were excluded from this literature search: ‘colonic irrigation’, ‘water birth’, ‘Kneipp therapy’, ‘spa therapy’, ‘whirlpool therapy’, ‘contrast baths’ and ‘balneotherapy’.

There is a lack of clarity in the usage of terms ‘hydrotherapy’ and ‘balneotherapy’ (Bender et al., 2005). Hydrotherapy uses water as a treatment, while balneotherapy uses natural thermal mineral water (Bender et al., 2005). Although these terms have often been used interchangeably, balneotherapy is not easily accessible to healthcare professionals, and so studies involving this treatment were excluded. Trials investigating solely the physiological responses (such as heart rate, blood pressure and renal function) of subjects immersed or exercising in water were also excluded.

The database search was supplemented by a manual search of: the Clinical Journal of Rheumatology, Annals of the Rheumatic Disease, British Medical Journal, Physiotherapy, Arthritis and Rheumatism, Rheumatology and Journal of Rheumatology and Physical therapy. Journals were searched from 1988 to September 2013, and were selected because they publish articles on rheumatological diseases. A further hand search of the bibliographic references in the extracted articles and existing reviews was also conducted to identify potential studies that were not captured by the electronic database searches. In addition, published theses in grey literature were examined to identify the relevant papers. To ensure that all of the relevant articles were obtained, an iterative process was used.

4.2.2 Inclusion and exclusion criteria for considering studies for this review

Studies were included if:

- They were randomised controlled trials (RCTs).
- They were published in the English language.
- They included participants aged 18 years or older who had been diagnosed with RA according to the 1987 ACR criteria (Arnett et al., 1988) or they used the criteria of Steinbrocker (Steinbrocker et al., 1949).
- A water-based intervention (hydrotherapy) was used in the study and compared with an alternative such as land therapy, home exercises, routine daily activities or standard physiotherapy.
- Patients had attended a minimum of four weeks' hydrotherapy intervention.
- They used one of the following outcome measures: pain, patient global assessment, activities of daily living (ADL), physical function, disease activities or QoL.

Articles were excluded if:

- They had insufficient information available (abstract only);
- They did not involve an RCT;
- They were not adult trials;
- They did not involve human trials;
- They included participants without rheumatic diseases;
- The treatment modality included balneotherapy, Kneipp therapy, mud therapy or sulphur therapy;

- They were not written in English (even if the abstract was in English).
- Participants were primarily and predominantly diagnosed with OA, fibromyalgia syndrome (FMS), back pain, neurological disease, or osteoporosis.

4.2.3 Assessment of the validity of the study

The researcher (KA) conducted the original search for the relevant articles and carried out the data extraction. The abstracts were reviewed first and, if deemed appropriate, the full papers were then reviewed and scored. The methodological quality of each study was reviewed by using the Physiotherapy Evidence Database (PEDro) scale (Maher et al., 2003). In addition, two researchers independently checked and confirmed the researcher's decisions regarding the inclusion of the relevant articles in the present review. Where decisions were unclear, they independently applied the inclusion/exclusion criteria to papers identified by the literature search, and classified the identified studies according to the predetermined criteria. A consensus method was used to solve any dispute regarding the inclusion or exclusion of a particular study. When there was disagreement, consensus was sought, but when disagreement persisted, a third independent reviewer made the final decision. The PEDro scale contains 11 items (Table 4.1, p.95). The first item represents the external validity of the trial. This item was not included in the calculation of the total PEDro score (maximum 10); therefore, the score in this study was based on items 2 to 11 and the PEDro score was thus a score out of 10. These items are scored either yes (1 point) or no (0-point). The individual item scores and the total PEDro scores have been shown to be reliable (Maher et al., 2003).

A study that scores 7 (scores positive in seven out of ten criteria) is considered to have a high methodological quality, a score of 5–6 a moderate methodological quality and a score between 0 and 4 is regarded as having poor methodological quality (Kollen et al., 2009; Maher et al., 2003; Moseley et al., 2002). The maximum achievable score for a high-quality study is 8 because it is difficult to blind either the therapist delivering the intervention or those participating in a hydrotherapy rehabilitation trial (Kollen et al., 2009; Maher et al., 2003; Sherrington et al., 2000).

4.3 Data collection and analysis

Articles fulfilling the inclusion criteria were subsequently assessed for methodological quality using the criteria list and operational instruction outlined and recommended by the PEDro for the quality assessment of RCTs (Maher et al., 2003; Sherrington et al., 2000). As shown in Table 4.1 (p.95).

4.4 Data extraction

To ensure that no significant information was omitted from the review, the researcher extracted data using a standardised form regarding: the author(s), place and date of publication, study design, sample size and percentage of female sample, mean age, the interventions, the type of outcome measures and follow-up/failure to follow-up.

Table 4.1: Criteria list for methodological quality assessment [Physiotherapy Evidence Database (PEDro)]. Adapted from Maher et al. (2003). Except the first item, each PEDro scale item achieved contributes 1 point to the total PEDro score (range 0–10 points).

Category number	PEDro Items	Answer
1	Eligibility criteria were specified	Y/N
2	Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	Y/N
3	Allocation was concealed	Y/N
4	The groups were similar at baseline regarding the most important prognostic indicators	Y/N
5	There was blinding of all subjects	Y/N
6	There was blinding of all therapists who administered the therapy	Y/N
7	There was blinding of all assessors who measured at least one key outcome	Y/N
8	Measurements of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Y/N
9	All subjects for whom outcome measurements were available received the treatment or control condition as allocated, or where this was not the case, data for at least one key outcome were analysed by ‘intention to treat’	Y/N
10	The results of between-group statistical comparisons are reported for at least one key outcome	Y/N
11	The study provides both point measurements of variability for at least one key outcome	Y/N
Key: Y = Yes; N = No		

4.5 Results

Two hundred and forty two studies were identified based on the key search terms and the hand search of bibliography references (CINAHL 22; Medline 47; PubMed 137; AMED 28; manual search eight). After the initial screening of the titles and abstracts, 34 studies were found to satisfy the inclusion criteria and were further scrutinised for the present systematic review (Figure 4.1, p.98).

Twenty-eight of 34 were excluded and reasons for exclusion are listed in Figure 4.1 (p.98). Data from six studies are presented in Table 4.2 (p.99 to 103).

Of the six studies included in this review, two were from the UK, two from Sweden, one from Finland and one from Canada. Studies were conducted as part of collaboration between physiotherapy and rheumatology departments (Eversden et al., 2007; Bilberg et al., 2005; Sanford Smith et al., 1998; Hall et al., 1996; Rintala et al., 1996; Stenström et al., 1991). One study compared hydrotherapy with no formal treatment (Rintala et al., 1996). All other studies compared hydrotherapy to single or multiple alternative interventions (Eversden et al., 2007; Bilberg et al., 2005; Sanford Smith et al., 1998; Hall et al., 1996; Stenström et al., 1991) (Table 4.2, p.99 to 103). None of the studies investigated costs. The PEDro scores for the present review ranged from 5 to 8 out of the maximum possible score of 10, without including the first item of the PEDro scale because it refers to external validity (Table 4.3, p.104) (Kollen et al., 2009; Maher et al., 2003).

4.6 Methodological quality of the studies

The methodological quality of the studies ranged from 5 to 8 on the PEDro scale of internal validity (Table 4.3, p.104), with a mean score of 6.8. Four studies were of high quality, whereas two were of moderate quality. Two studies (Sanford Smith et al., 1998; Stenström et al., 1991) failed to report or describe whether an intention-to-treat analysis or concealment of the treatment allocation was used. In three studies (Eversden et al., 2007; Hall et al., 1996; Sanford Smith et al., 1998), the outcome assessor was blinded to the intervention. While all of the participants were randomised in the included trials, only three studies (Bilberg et al., 2005; Eversden et al., 2007; Hall et al., 1996) specified the methods used. Two studies used optimal allocation using a computer programme (Bilberg et al., 2005; Eversden et al., 2007) and one used block randomisation (Hall et al., 1996).

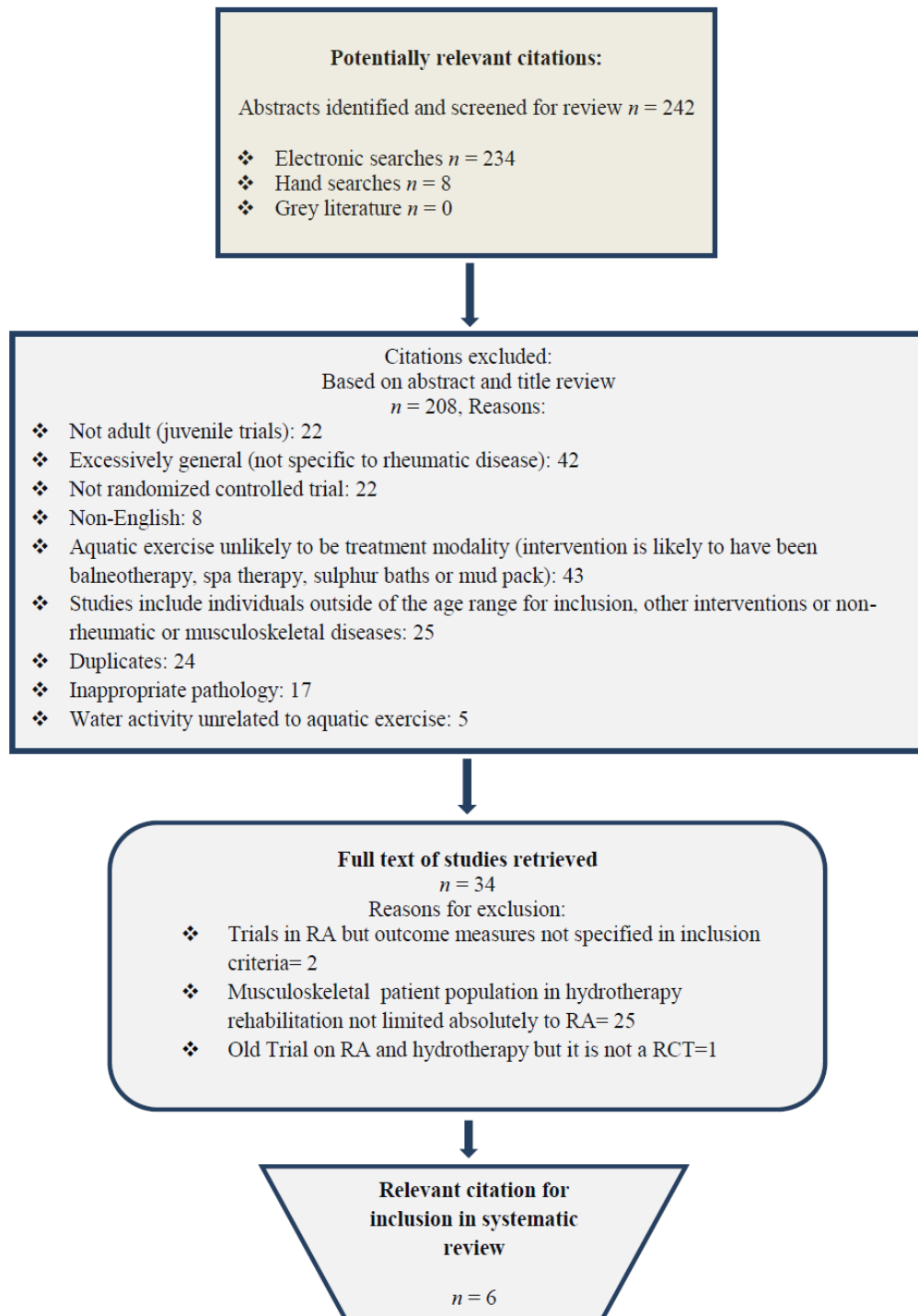


Figure 4.1: Flowchart of the literature search.

Table 4.2: Summary of studies meeting the selection criteria for inclusion in the systematic review for RA.

Authors, country, year of study	Sample n female %	Study design	Drop outs	Mean age (SD) in years	Intervention/ duration/ programme setting	Outcome measures	Patient assessment/ follow up	Results/comments
Hydrotherapy versus land-therapy								
Hall et al., 1996; UK	139 (66%)	RCT	1	58.2 (11.1)	<p>A: Aquatic exercise 30 minutes twice weekly for 4 weeks.</p> <p>B: Supervised land-based exercise.</p> <p>C: Supervised seated water immersion.</p> <p>D: Supervised land relaxation.</p>	<p>Pain using McGill questionnaire.</p> <p>Ritchie articular index (RAI).</p> <p>Morning stiffness duration.</p> <p>Grip strength (digital monitor inflated to 20 mm Hg).</p> <p>Wrist and knee ROM using a standard goniometer.</p> <p>AIMS2 for health status.</p> <p>Patient perception.</p>	<p>Baseline</p> <p>4 weeks post treatment</p> <p>3 months follow-up</p>	<p>No significant differences between groups in terms of pain (all patients demonstrated a significant pain reduction ($p \leq 0.005$)).</p> <p>All groups have significant reduction in joint tenderness between pre and post treatment with greater reduction in the hydrotherapy group ($p = 0.03$).</p> <p>Grip strength, wrist ROM, duration of morning stiffness, and CRP levels did not change significantly ($p \geq 0.05$).</p> <p>Significant increase in knee ROM occurred mainly in women with hydrotherapy group ($p \leq 0.02$).</p> <p>Significant improvement in mood and tension occurred for all patients after treatment and in follow up for all groups markedly in women ($p = 0.02$). At follow up, greater effect in hydrotherapy group ($p = 0.03$).</p> <p>All groups reported similar perceptions of the effectiveness of the interventions at pre-test and post-test ($p \leq 0.0001$).</p>

Table 4.2 (Continued): Summary of studies meeting the selection criteria for inclusion in the systematic review for RA.

Authors, country, year of study	Sample n female %	Study design	Drop outs	Mean age (SD) in years	Intervention/ duration/ programme setting	Outcome measures	Patient assessment/ follow up	Results/comments
Eversden et al., 2007; UK	115 (69%)	RCT	30	55.2 (13.3)	A: Hydrotherapy – One session/week for six weeks; pool at 35°C. B: Supervised land exercise.	Primary outcome measure was self-rated overall effects on a Likert 7-point scale. Secondary outcome measure included: VAS pain, ten-meter walk speed, HAQ, EQ-5D utility, EQ-VAS.	Baseline Post-treatment (six weeks) Follow-up (three months)	Patients in the hydrotherapy group felt very much better in their overall health status compared to patients treated in the land exercise group ($p < 0.001$). No significant differences between groups in terms of changes to HAQ ($p = 0.09$), EQ-5D utility score ($p = 0.61$), EQ-VAS ($p = 0.57$) or pain VAS ($p = 0.40$).
Stenström et al., 1991; Sweden	60 (86%)	RCT	5	52 (11.2)	A: Hydrotherapy – One session/week in group of five, for 40 minutes, for four years in temperature of 34°C (each year there is a two-and-a-half-month vacation). B: Supervised standard physiotherapy on land.	Ritchie's articular index for disease activity. Larsen radiological index. Laboratory inflammatory markers Sphygmo-manometer cuff for grip strength. VAS for pain. Functional tests such as outdoor walking, indoor walking, lifting, leaning forward and rising. Two open-ended questions about activity level/exercise habits.	Post training (four years)	No significant difference between the groups in Ritchie's articular index, Larsen's radiological index, soft tissue swelling or laboratory markers ($p > 0.05$). Improved right-hand grip strength in hydrotherapy group ($p \leq 0.01$); decreased left hand grip strength in comparison group ($p > 0.05$). No significant difference between the groups in VAS or functional tests ($p > 0.05$). Significant difference in activity levels between the hydrotherapy group compared with comparison group ($p \leq 0.01$). Two-year follow-up at the end of the training period; the difference between the hydrotherapy and comparison groups was significant ($p \leq 0.001$).

Table 4.2 (Continued): Summary of studies meeting the selection criteria for inclusion in the systematic review for RA.

Authors, country, year of study	Sample n female %	Study design	Drop outs	Mean age (SD) in years	Intervention/ duration/ programme setting	Outcome measures	Patient assessment/ follow up	Results/comments
Hydrotherapy versus home exercise programme								
Sanford Smith 1998; Canada	24 (75%)	RCT	4	58.4 (11.6)	A: Hydrotherapy three times/week for 10 weeks. B: Home exercise programme.	AJC ESR Grip strength measured using Martin Vigorimeter (Hillside Medical Supplies Limited, Nottingham, UK). HAQ for function. Treadmill stress test.	Baseline (one week prior). One week after 10 weeks' exercise period. No follow up	There were no between-group differences; however, both groups showed a similar decrease in AJC and ESR ($p \geq 0.05$). Both groups demonstrated an improvement in grip strength ($p \leq 0.05$), but there was no significant difference between the groups. Both groups showed an increase in exercise tolerance ($p \leq 0.05$). HAQ result showed a statistically significant improvement in two components of HAQ in the control group ($p \leq 0.05$) and no significant improvement in the aqua-aerobics group ($p \geq 0.05$). No significant between-group effects for duration or peak workload on treadmill ($p \geq 0.05$).

Table 4.2 (Continued): Summary of studies meeting the selection criteria for inclusion in the systematic review for RA.

Authors, country, year of study	Sample n female %	Study design	Drop outs	Mean age (SD) in years	Intervention/ duration/ programme setting	Outcome measures	Patient assessment/ follow up	Results/comments
Bilberg et al., 2005; Sweden	47 (89%)	RCT	4	49	<p>A: Hydrotherapy twice weekly for 12 weeks in a group of eight or nine, for 45 minutes, experiencing moderate aerobic intensity.</p> <p>B: Home exercise programme and routine daily activities.</p>	<p>Sub-maximum ergometer cycle (Åstrand, Varberg, Sweden) for aerobic capacity as primary outcome measure.</p> <p>SF-36 for health status as primary outcome measure.</p> <p>Chair test as secondary outcome measure.</p> <p>Shoulder endurance test as secondary outcome measure.</p> <p>Grip strength (using electronic instrument, Grippit).</p> <p>HAQ for functional disability and AIMS2 for QoL.</p>	<p>Baseline</p> <p>Post treatment (3 months)</p> <p>6 months follow-up for hydrotherapy group</p>	<p>No significant changes were found for the primary outcome measure between baseline and post-treatment ($p \geq 0.05$).</p> <p>At follow up, SF-36 showed significant improvement within the training group ($p < 0.05$); no significant changes were found in between-group differences ($p \geq 0.05$).</p> <p>Performance on the chair test increased significantly in the training group compared with the control group ($p = 0.005$).</p> <p>Performance on the shoulder endurance test increased significantly in the training group compared with the control group ($p \leq 0.001$).</p> <p>Grip strength of the left hand increased significantly in the hydrotherapy group compared with the home exercise group ($p \leq 0.001$).</p> <p>AIMS-2 and HAQ displayed a significant within-group improvement ($p = 0.007$ and 0.04, respectively), but there was no significant differences between the groups ($p \geq 0.05$).</p>

Table 4.2 (Continued): Summary of studies meeting the selection criteria for inclusion in the systematic review for RA.

Authors, country, year of study	Sample n female %	Study design	Drop outs	Mean age (SD) in years	Intervention/ duration/ programme setting	Outcome measures	Patient assessment/ follow up	Results/comments
Hydrotherapy versus control (no formal treatment)								
Rintala et al., 1996; Finland	34 (85%)	RCT	0	48 (10)	A: Aquatic exercise 45-60 min twice a week for 12 weeks, pool temperature 30°C. B: Unsupervised routine daily activities.	VAS pain. Joint mobility by using signals of functional impairment. Muscle strength & endurance by using digital dynamometer.	Baseline Post-treatment (12weeks) No follow up	Pain more diminished in experimental group than in control group ($p \leq 0.05$). Joint mobility improved in experimental group ($p \leq 0.05$). Muscle strength and endurance improved in experimental group compared with control group ($p \leq 0.001$).
Key: AIMS2 = Arthritis Impact Measurement Scale version 2; AJC =Active-Joint Count; CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; HAQ = Health Assessment Questionnaire; SF-36 = Short Form (36); VAS = Visual Analogue Scale. A: Hydrotherapy group; B: Comparator groups								

Table 4.3: Methodological quality using the Physiotherapy Evidence Database (PEDro) scale scoring the items out of 10.

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total score (/10)
Stenström et al. (1991)	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5/10 moderate quality
Hall et al. (1996)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10 high quality
Rintala et al. (1996)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10 high quality
Sanford Smith et al. (1998)	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5/10 moderate quality
Bilberg et al. (2005)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10 high quality
Eversden et al. (2007)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10 high quality
Key: Y, yes (= 1); N, no (= 0)												

4.6.1 Participants

The six studies described above included both men and women (total no = 419); 326 (78%) of the participants were women. The participants' age across the studies ranged from 18–80 years. The average number of participants in the treatment group post-randomisation and before any withdrawals was 29 and ranged between 12–57, with only three studies having groups with more than 30 participants (Eversden et al., 2007; Hall et al., 1996; Rintala et al., 1996).

4.6.2 Interventions summary

Hydrotherapy versus land therapy

Hall et al. (1996) tested the hypothesis that the combined effects of water immersion and exercises in that water were therapeutically superior to either modalities used singly. They did this by designing a parallel RCT randomising all the participants in four groups (hydrotherapy, seated immersion, land exercise and land relaxation). Hall et al. (1996) showed that all the four groups showed physical and emotional improvements.

Hydrotherapy proved superior in improving the physical and emotional aspects of patients with RA. AIMS-2 measured mood and tension, and patients in each of the four groups improved significantly over time, but a greater effect of improvement in mood and tension was found in women. During the follow-up period, participants continued to experience significant improvement, but the participants in the hydrotherapy group reported the greatest effect. Participants in all the four groups reported reduction in joint tenderness over time. However, participants in the hydrotherapy group show the greatest reduction.

Eversden et al. (2007) evaluated the effects of hydrotherapy with exercises versus land exercises on the overall response to treatment, physical function and QoL of patients with RA. These authors designed a programme of 30-minute hydrotherapy sessions once a week for six weeks (at 35°C) with a control group on land-based programme for six weeks. Patients were randomly allocated to hydrotherapy or land-based exercises using sealed opaque envelopes that indicated their treatment allocation. The participants performed warm-up exercises for ten minutes using mobilising and stretching exercises. The core exercises, repeated ten times a week, focused on joint mobility, muscle strength and functional activities.

The primary outcome measure applied in this study was self-rated QoL, in which the effect of treatment was measured as the change on a seven-point scale ranging from 1 (very much worse) to 7 (very much better) (Richards & Scott, 2002). Secondary outcomes were collected at baseline, both on the day of the last treatment session and three months post-treatment. Pain was assessed using a 10-cm VAS, where 0 cm represented no pain and 10 cm represented severe pain (Langley & Sheppeard, 1984). Physical function was assessed using the HAQ (Bruce & Fries, 2005; Felson et al., 1993; Fries et al., 1980). The ten-metre walk speed test was used to assess lower-limb function. This test was previously used for patients with neurological problems and had been used by Eversden et al. (2001), who carried out the previous pilot study (Eversden, 2001). The primary outcome measure of Eversden et al. (2007) showed that RA patients who attended outpatient clinics were more likely to report feeling much better or very much better if they were treated with hydrotherapy (40/46, 87%) than if they were

treated with exercises on land (19/40, 47.5%) ($p < 0.001$ Fisher's exact test). This benefit was reported immediately after completion of the treatment. There was no difference between treatment groups in the secondary outcome measures. In the follow up period of three months, no significant differences were observed in either primary or secondary outcome measures.

A Scandinavian study (Stenström et al., 1991) failed to show any statistically significant differences in pain rating, functional outcomes tests (Stenström, 1990), Ritchie's articular index (Ritchie et al., 1968), Larsen's radiological index (Larsen et al., 1977), soft tissue swelling and laboratory parameters between the hydrotherapy group and a comparator group. Participants answered a questionnaire using self-reported questions with two open-ended questions on exercise habits e.g. 'what do you think is positive regarding the training?' and 'what do you think is negative regarding the training?'.

Doleys et al. (1982) were the first to use these self-reported questions on exercise habits for training patients with chronic pain. Post-treatment, four out of 27 participants in the hydrotherapy group stated that they never or seldom exercised (in addition to the training protocol) compared to 16 out of 28 participants in the comparator group. This indicated that there was a statistically significant difference in their response on exercise habits between the hydrotherapy group compared with the comparator group (supervised standard physiotherapy) ($p \leq 0.01$). Similarly, the two years follow-up data showed that two out of 27 of the hydrotherapy group and 16 out of 28 in the comparator group stated that they never or seldom exercised, indicating that there was a statistically significant

difference in the response about exercise habits between the hydrotherapy and the comparator group (supervised standard physiotherapy) ($p \leq 0.001$).

Hydrotherapy versus home exercise (HE) programme

Sanford Smith et al. (1998) recruited 24 participants (19 of them females) with a mean age of 58.4 years to participate in their study. Subjects were randomly allocated to the hydrotherapy group or the home exercise group. The hydrotherapy sessions were held three times a week for 10 weeks. Each session consisted of an hour of exercises performed in a hydrotherapy pool heated to 36°C. Fifteen minutes of warm-up aerobic stretches for the spine, chest and extremities was followed by 20-25 minutes of aerobics exercise. Participants exercised to a maximum target heart rate of 70% exercise tolerance (Ekblom et al., 1974; Minor et al., 1988; Nordemar et al., 1981). The other group participants received a ROM exercise and isometric strength exercises programme for ten weeks. Nonetheless, the results failed to reveal a differential effect between the hydrotherapy and home exercise group. Moreover, there was no improvement in functional ability measured by HAQ.

Bilberg et al. (2005) hypothesised that three months of hydrotherapy would improve patients' aerobic capacity, functional ability and perception of physical health. Forty-seven participants (42 women) were divided into two groups (the hydrotherapy group and the home exercise group). The treatment group exercised twice a week for 12 weeks in groups of eight or nine patients in a temperate pool. The duration of each session was 45 minutes and the exercise was of moderate

aerobic intensity. The patients in the home exercise group continued with their usual daily activities and were prescribed a home exercise programme (HEP).

Outcome measurements were carried out at baseline and at three months post-intervention for both groups. The patients in the hydrotherapy group were followed up for six months after completion of the study. Aerobic capacity was estimated using a sub maximum ergometer cycle (Bilberg et al., 2005), and the physical component of the Short Form (36) (SF-36) was chosen as the primary outcome measure.

The study was unable to confirm whether the intervention was effective in improving aerobic capacity and QoL. However, the differences showed significant improvement in the hydrotherapy group for the secondary outcome measures – isometric shoulder endurance, grip force, dynamic endurance of the lower extremities (chair test) and muscle function of the lower extremities – compared with the home exercise group. The chair test was assessed by counting the maximum number of times that the patient was able to get up from a chair during one minute (Mannerkorpi & Ekdahl, 1997). The isometric shoulder endurance test, which is used to measure the isometric endurance of the shoulder abductor muscles, was assessed by monitoring the maximum length of time that a person was able to hold his/her arm at 90 abduction with a 1-kg cuff attached proximally to the wrist joint (Mannerkorpi et al., 1999), and was carried out at baseline and three months post-treatment. The differences in all of the primary and secondary outcome measures between baseline and 6 months follow-up were statistically significant within the hydrotherapy group, with the exception of aerobic capacity.

Hydrotherapy versus control

Rintala et al. (1996) studied the effects of hydrotherapy on chronic pain and functional performance in patients with RA. Pain was assessed using VAS. Functional performance was assessed by measuring joint mobility, muscle strength and endurance.

Thirty-four participants were randomly allocated to aquatic exercise (n = 18) or the routine daily activities group (n = 16). The aquatic exercise group undertook muscle strength, endurance, and joint mobility exercises in sessions lasting between 45 and 60 minutes, twice a week for 12 weeks. The routine daily activities group participated in their daily activity with no additional exercise during the study period. The major findings of this study at the end the 12-week training period were that the hydrotherapy group experienced less pain, increased muscle strength and increased endurance compared to the routine daily activities group. It seems that the type and duration of the training provided in this study was sufficient to maintain joint mobility in the hydrotherapy group.

4.6.3 Outcome measures

RA affects physical, social and psychological aspects of patients' health status or QoL. The outcome measures that were used in the included studies reflected one or more of the variables (Fitzpatrick et al., 1992; Hakala, 1997).

4.6.3.1 Pain

A pain scale was used in all the reviewed studies. Scores on these scales were measured before and after the intervention. Various instruments were used to measure pain. The 10-cm visual analogue scale (VAS) was the tool used the most

commonly in three studies (Eversden et al., 2007; Rintala et al., 1996; Stenström et al., 1991). Another instrument that was used by Hall et al. (1996) to assess pain was the McGill Pain Questionnaire. The pain subscales from a variety of self-reported questionnaires were also used, such as the Arthritis Impact Measurement Scale (AIMS) (Hall et al., 1996), Health Assessment Questionnaire (HAQ) (Bilberg et al., 2005; Eversden et al., 2007; Sanford Smith et al., 1998), and the SF-36 (Bilberg et al., 2005).

Rintala et al. (1996) used pain as a primary outcome measure and found that there was a statistically significant reduction in the pain level after use of a water exercise programme in patients with RA compared to the control group. None of the studies used pain as an outcome measure for a power calculation to determine the sample size.

4.6.3.2 Physical function

HAQ and VAS were the most commonly used instrument in the reviewed studies (Bruce & Fries, 2005; Felson et al., 1993; Fries et al., 1980). They were used in three studies (Bilberg et al., 2005; Eversden et al., 2007; Sanford Smith et al., 1998). However, only one of these (Bilberg et al., 2005) found a significant improvement observed in physical function compared with the home exercise group. HAQ was used as a primary outcome measure in one study (Sanford Smith et al., 1998). Sanford Smith et al. (1998) showed a trend for an improvement in physical function using the total HAQ score in the aqua-aerobics group compared with the home exercise group but this was not statistically significant.

4.6.3.3 Health status

Three studies (Bilberg et al. 2005; Eversden et al., 2007; Hall et al. 1996) investigated health status using three different types of questionnaires (SF-36; EQ-5D and AIMS-2, respectively). Eversden et al. (2007) showed that there was no statistically significant difference in EQ-5D scores between hydrotherapy and land-based exercise. Bilberg et al. (2005) showed that in the hydrotherapy group, whilst there was a significant within-group improvement in SF-36 scores over time, these differences were not statistically significant when compared to the home exercise group. Finally, Hall et al. (1996) reported significant improvement in the level of tension and mood for all participants in all groups over time; although at three months follow-up, patients receiving hydrotherapy demonstrated the greatest improvement effect in the level of tension and mood.

4.6.3.4 Disease activity

In terms of disease activity, a variety of categories, such as MS, joint tenderness, joint swelling, grip strength and laboratory markers [acute phase reactant such as C- reactive protein (C-RP)], were measured separately in four studies (Bilberg et al., 2005; Hall et al., 1996; Sanford Smith et al., 1998; Stenström et al., 1991). The results of Bilberg et al. (2005) indicated that grip strength of the left hand increased significantly in the hydrotherapy group compared with the home-exercise group ($p < 0.001$). This contrasted with the findings of Hall et al. (1996) and Sanford Smith et al. (1998), who did not find any significant difference between the hydrotherapy group and home exercise group in terms of grip strength, duration of MS and C-RP level or Erythrocyte Sedimentation Rate (ESR – a blood marker of inflammation) ($p > 0.05$). In Stenström et al. (1991), the right-

hand grip strength of participants improved significantly in the hydrotherapy group ($p \leq 0.01$), while in the standard physiotherapy group, participants' left-hand grip strength deteriorated ($p \geq 0.05$). Hall et al. (1996) also showed that all patients have significant improvement in joint tenderness between pre- and post-treatment, but that patients in the hydrotherapy group had the greatest reduction in joint tenderness between pre- and post-treatment.

4.6.3.5 Patient perception

Patients' perception of hydrotherapy treatment was investigated in two studies (Eversden et al., 2007; Hall et al., 1996). Hall et al. (1996) used a five point Likert-type perception scale, which was designed by Langley and Sheppard (1984), their findings were unexpected and showed that all groups reported similar perceptions of the effectiveness of the intervention with overall mean ratings (on a 1-5 scale) of 3.6 (SD 0.9) at pre-test and 3.4 (SD 1.15) at post-test. Eversden et al. (2007) used a seven-point Likert scale and their findings showed that the largest set of significant clusters of feeling 'very much better' was in the hydrotherapy group compared with the land exercise group.

After reviewing all six studies, neither meta-analysis nor statistical pooling were considered because of the heterogeneity among the studies, including the small sample size, variations in symptoms and duration, interventions and the reporting of the outcomes.

4.7 Discussion

The objective(s) of the present systematic review was to evaluate the available evidence for the effectiveness of hydrotherapy in the treatment of RA patients

compared to an alternative. These findings suggest that patients who received hydrotherapy treatment for RA gained some beneficial effects in improving their health status (for example reduced pain scores). Further additional benefits included a substantial increase in physical activity and emotional wellbeing in patients in the aquatic programmes compared with control groups in the short term. There is no cure for RA, and it is therefore important to look into non-pharmacological treatment that reduces the disease progression. A treatment for RA that reduces or slows down the inflammatory process would be of great benefit, both from a health service perspective and also from the perspective of the RA patient, in terms of the perceived benefit to improving their QoL.

The PEDro scores for the papers reviewed ranged from 5-8 and were regarded as being of moderate to high quality. The average methodological quality of all the studies was 6.8 and was regarded as moderate. However, all of the studies reviewed suffered from methodological flaws that limited their generalisability to the wider population of RA patients. These limitations included lack of control group in the follow-up period in the study of Bilberg et al. (2005); inappropriate primary outcome measures in the study of Eversden et al. (2007); small sample size in the study of Rintala et al. (1996) and Sanford Smith et al. (1998); and finally, poor concealment allocation in the study of Stenström et al. (1991) and Sanford Smith et al. (1998).

The six studies that were appraised differed in the frequency and duration of the hydrotherapy sessions given to participants: twice weekly over four weeks, once weekly over six weeks, three times weekly over ten weeks, twice weekly over 12

weeks and once weekly over four years (long term study). Therefore, we are unable to determine from the present review the ideal number of hydrotherapy sessions that are needed for RA patients to derive clinically significant benefits from this intervention. A possible explanation for this might be that each study was designed with specific targets and goals, and different primary outcome measures. A recent national survey in the UK by HyDAT Team (2009) reported that the median optimal number of sessions for the treatment of RA patients were six sessions.

4.8 Methodological critique of the reviewed articles

The choice of outcome measures used in the reviewed studies should be examined with caution. The Health Assessment Questionnaire (HAQ) was the most common instrument used to measure physical function. In terms of the efficacy of hydrotherapy, it was used as a primary outcome measure in only one study (Sanford Smith et al., 1998). Significant improvements in health status (health-related QoL (EQ-VAS) were found in two studies (Bilberg et al., 2005; Hall et al., 1996) by using two different health-related QoL scales of measurement. This means that a standardised, specific scale, superior to any other, was not used when measuring health status or QoL in RA patients.

Grip strength and joint tenderness were the most frequent disease activity indices, and were examined in three studies – Bilberg et al. (2005); Hall et al. (1996); Stenström et al. (1991). The contradictory results of grip-strength measures can be explained by the different methods of assessment tools employed in various studies. Hall et al. (1996) measured the grip strength of the dominant hand by

using a digital grip strength monitor inflated to 20 mm Hg (Rhind et al., 1980). The mean of three readings was recorded, whereas Bilberg et al. (2005) measured grip strength by using an electronic instrument (Grippit, manufactured by AB Detektor in Göteborg, Sweden), recording the maximum and mean strength and the best performance of three (Nordenskiöld, 1990). Conversely, Stenström et al. (1991) measured grip strength manually by using a sphygmomanometer cuff rolled up two turns and inflated to 20mm Hg (Lansbury, 1958). Sanford Smith and colleagues (Sanford Smith et al., 1998) did not report the method of assessment used to measure the grip strength. Therefore, future studies should consider using an appropriate procedure in measuring grip strength in patients with RA with dexterity malfunction and pain.

The reduced joint tenderness observed in the hydrotherapy group of Hall et al. (1996) might be attributed to the reduction in joint loading supported by buoyancy. Furthermore, the hydrostatic pressure of water immersion is considered effective in reducing oedema (Poyhonen et al., 2000). These findings will help researchers to assess different aspects of the underlying disease due to high variability of the disease presentation and progression.

It was noted that there were many substantial methodological shortcomings in the research that had been reviewed, mainly in the inadequate reporting of interventions in terms of their settings, water temperature, depth of pool, and the type and intensity of the exercise programme. In addition, there were other methodological flaws relating to RCT design, such as inappropriate randomisation, concealment of allocation to groups, and the blinding procedure to

the outcome measurements. Moreover, some of the studies did not give detailed information about their data analysis. This might have affected the conclusions drawn from these studies, so caution is required in the interpretation of their findings. Lastly, the variation in the dosages of intervention in the six studies makes it difficult to provide clear guidance in this area. Overall, many of the studies involved in the present review had a relatively small sample size and lacked adequate statistical power to examine the effectiveness of hydrotherapy intervention in the treatment of patients with RA. In addition, the studies reviewed used different primary outcome measures and a few studies had inadequate and variable follow-up periods.

The present review had several limitations. Firstly, the review focused only on studies published in English, and therefore potentially relevant articles that have been published in other languages may have been missed. Such studies were excluded because of the limited resources available for translation. Secondly, the searches were limited to already-published articles because all such papers had been peer-reviewed, which ensures their good quality and thus improves external validity. Thirdly, the cost effectiveness (CE) of hydrotherapy was not investigated and therefore not featured in the review. Unfortunately, none of the studies reviewed reported the cost-effectiveness of their intervention. Costs-versus-benefits assessment will become increasingly important in medical rehabilitation and physiotherapy research, as RA patients are more likely to continue to use healthcare services for a long period because of the chronic nature of the condition. Therefore, future studies should consider the cost-effectiveness of hydrotherapy intervention for patients with this condition.

4.9 Implications for practice

The results of the present review indicate the beneficial effects of hydrotherapy compared with an alternative intervention such as land-based therapy, home-exercise or daily routine activities. An important practical implication is that the outcome measures used to assess pain, physical function, disease activity and QoL scales are appropriate for the assessment of patients with RA. In addition, some of the studies reviewed showed that hydrotherapy is an effective intervention to alleviate the symptoms associated with RA such as pain, disease activity (grip strength, joint tenderness) and health status (mood and tension). The evidence from this review might give further option for rheumatologists to refer appropriate RA patients for hydrotherapy treatment as part of their medical rehabilitation.

4.10 Implications for research

Few RCTs have examined the effects of a hydrotherapy intervention on RA. The present review indicated that there is no consistency in the literature in terms of the type of exercise and the dose (intensity, frequency and duration) used in hydrotherapy treatment for patients with RA. In addition, future studies should consider examining the CE of hydrotherapy and the optimal use of aquatic exercise for patients with RA. Considerably more work is needed to determine the effectiveness of hydrotherapy on disease activity, psychological aspects of RA (anxiety and depression), and physical function using appropriate outcome measures. Large, high-quality RCTs using rigorous methodology (such as adequate sample size) are needed due to the fact that they could provide more definitive evidence for the efficacy of hydrotherapy.

4.11 Conclusions

There is some evidence to suggest that hydrotherapy is an effective modality for reducing pain and improving the health status of patients with RA in the short-term. However, the long-term benefits of hydrotherapy are presently unknown. It is difficult to make specific recommendations at this stage because of lack of evidence (such as optimal duration and frequency) for clinical practice because of the heterogeneous nature of the interventions. Therefore further studies are needed using robust RCTs.

The next chapter discusses the methodology giving a description of the patient sample, patient-recruitment process and hospitals involved. It provides a description of the development and application of the treatment protocol prescribed to the intervention groups in the RCT Study One.

CHAPTER FIVE: METHODOLOGY OF RANDOMISED CONTROLLED TRIAL (RCT) (STUDY ONE)

5.1 Introduction

This chapter describes the methodology for the single blind randomised-controlled trial (RCT) set out in this thesis. The methodology in this chapter illustrates the development and application of the treatment protocol prescribed for the hydrotherapy and land-therapy group. It also describes the preparation carried out prior to data collection: patient sample; patient recruitment process; referral process and amendments. Ethics committee approval was obtained and the pilot study performed. Details of how the challenges within the hospitals involved were addressed and the rationale behind the choice of outcome measures was provided. It is presented according to the 2010 CONSORT statement (Schulz et al., 2010).

Aims of Study One

Primary Aim: The primary aim of the RCT Study One was to:

- Evaluate the difference in outcomes for RA patients when treated with hydrotherapy as opposed to land based therapy.

Secondary Aims: The secondary aims of the RCT Study One were to:

- Identify and evaluate the differences in demographic factors between the hydrotherapy and land-therapy groups.

- Identify and understand the reasons for the difference in functional ability measured by HAQ-DI between those receiving hydrotherapy and those receiving land therapy.
- Evaluate whether or not hydrotherapy could improve pain and GWB, health-related quality of life (HRQoL), disease activity and mood symptoms (depression and anxiety) more effectively than land therapy in patients with RA.
- Determine the association between variables measuring disease activity.
- Determine the association between variables measuring psychological status with socio-demographic features and disease activity indices.
- Determine which factors predict functional disability.

5.2 Methods

5.2.1 Research design

In order to compare the effect of two different interventions, using two independent groups, simultaneously, over time, a parallel, longitudinal, randomised and controlled trial was carried out. Because of the interventions studied [hydrotherapy and land-based therapy] involving therapist-patient interaction, it was only possible to blind the researcher; the study was therefore classed as single blind.

5.2.2 Participants

According to the aims of the study, all RA patients referred and eligible for hydrotherapy were invited into the study. The recruitment for this study utilised a

gatekeeper approach, wherein the health professional involved in the potential participants' care approached the participant (who fulfilled inclusion/exclusion criteria) on behalf of the researcher. There were no financial incentives and therefore no coercion. The hospital was paid for the services provided for the pool time to avoid delay for participants involved in the trial.

5.2.2.1 Inclusion and exclusion criteria

The samples of 86 RA patients were identified based on the following inclusion and exclusion criteria:

5.2.2.1.1 Inclusion criteria

- Age ≥ 18 years. This age and above differentiates adult onset of RA from juvenile rheumatoid arthritis (JRA). The trial included adult RA only.
- Males and females.
- All patients referred to physiotherapy with a diagnosis of RA.
- Patients on a stable drug regimen for at least 2 weeks for NSAIDs and at least 6 weeks for DMARDs.
- Treatment by corticosteroid orally or injection permitted during the study. Drug changes were permitted to emphasise the realistic nature of the clinical management of RA.

5.2.2.1.2 Exclusion criteria

Patients with history of any known condition contraindicated to aquatic physiotherapy (such as myocardial infarction, fear of water, uncontrolled epilepsy,

chlorine sensitivity, infected open wound, uncontrolled HT and incontinence of faeces) were excluded (Edl et al., 2004; Eversden et al., 2007; Schrepfer, 2002).

5.2.2.2 Recruitment of rheumatologists

Two consultant rheumatologists working at the Kellgren Centre Rheumatology department within the CMFT agreed to refer patients to the study, and another consultant rheumatologist from the SRFT agreed to refer patients to the study. A presentation and a letter to clinicians (Appendix 1) were prepared and sent to them illustrating the aims, protocol, design methodology and outcome measures intended as a proposal to invite the consultants to be part of study team. All Rheumatologists used the ACR criteria (Arnett et al., 1988) to diagnose RA (Table 2.1, p.33). The ACR/European League against Rheumatism updated their diagnostic criteria in 2010 (Aletaha et al., 2010) (Table 2.2, p.34). This considered four additional criteria, which can be applied to any patient. All consultants agreed to use these criteria for diagnosis of RA and permitted their patients to be randomly allocated to either the hydrotherapy or the land-therapy group.

5.2.2.3 Recruitment of rehabilitation staff

Two specialist physiotherapists who were working in rheumatic rehabilitation, one from CMFT and one from SRFT, agreed to participate in this trial. A presentation was given in each department to explain the goals, impacts, procedure and methodology of the study, and possible difficulties that might be faced during the trial. After which all the personnel present agreed to partake and allowed their patients to be randomly allocated to either group.

5.2.2.4 Treatment sites

Treatment for the hydrotherapy and land exercise group was offered on the two sites because participants were recruited from the two hospitals, which were spread over a wide geographical area around Greater Manchester. The researcher observed and followed treatment sessions between sites as part of quality assurance.

5.2.2.5 Trust staff arrangement

Overall management of the study was the responsibility of the researcher, but because each Trust had a specific policy and protocol for research and development (R&D), the researcher contacted individuals in each trust to find out their requirements for R&D. The Director of Studies (DoS) assisted the researcher only with the discussions, which were necessary to have with each Trust, in order to decide study-funding issues. Each Hospital Trust had individual requirements for payment for participants and the Trust logo was required on every study document. After the approval of the main NHS Ethical Committee (Appendix 15), other approvals were obtained from each R&D Trust office (Appendix 16&Appendix 17). The researcher attended the Good Clinical Practice (GCP) course required for anyone who wishes to carry out NHS research.

5.2.2.6 Researcher responsibility

The researcher was responsible for the day-to-day running of the study. Prior to beginning the recruitment process, the researcher had visited the hydrotherapy pool and observed treatment protocols in order to understand their responsibilities

before designing the treatment protocol and embarking on their research. The researcher was responsible for sending and collecting questionnaires and, after interventions, inputting all the data onto the Statistical Package for the Social Sciences (SPSS). He organised the production and printing of all the necessary study documents (Appendix 2 –10). The researcher was in close contact with the three consultant rheumatologists and physiotherapists to take care of any issues concerning the participants or provide updates on the rehabilitation programme.

5.2.3 Interventions

5.2.3.1 The referral process

Figure 5.1 (p.130) illustrates all stages of the referral process in this study.

5.2.3.1.1 Pre-trial stage

RA patients who were suitable for the study were referred to physiotherapy by the consultants' rheumatologist. The rheumatology physiotherapy team performed an initial assessment to decide whether the participants were eligible for the study or not, depending on the inclusion and exclusion criteria. If they were eligible and agreed to take part, they signed a data access sheet (Appendix 2). In addition, a participant information sheet (Appendix 3) was provided 48 hours prior to their next physiotherapy appointment to allow a consultation period. If they were ineligible or unwilling to participate normal treatment was resumed with no further information on the study. The researcher contacted the willing participants by phone to inform them of the next step in the procedure – the questionnaires and

consent forms. The researcher received written consent (Appendix 4) and all the completed questionnaires by the time of the second physiotherapy appointment.

5.2.3.1.2 Assessment stage

After the initial physiotherapy assessment performed at the first appointment, the rheumatic physiotherapy team, using block randomisation by an independent coordinator, assigned each patient to one of two groups. All participants were given further advice and an appointment was made for their next treatment [either hydrotherapy or land therapy] depending on the randomisation. The researcher was blinded to the process of randomisation.

5.2.3.1.3 Trial stage

All participants completed outcome measures (five questionnaires) before the intervention (Test 1). The intervention started one week following randomisation. The intervention programme was for six weeks with one session per week. Both the hydrotherapy and land-based exercises consisted of warm-up, ROM, sustained stretching exercise, core stability, balance exercise and strengthening exercise (Appendix 12, 13).

Design and development of intervention exercise protocol

There has been little agreement to date on what evidence there is to suggest that exercise for RA patients improves general muscular endurance and strength without detrimental effects on disease activity or pain (Hurkmans et al., 2009). It has been demonstrated in the past that RA patients should be careful to use only the exercise prescribed because of issues of disease activity and potential

exacerbation of symptoms (Heine et al., 2012). However, recent evidence suggests that exercise does not have a negative impact on the disease process, and may in fact be beneficial (Hurkmans et al., 2009), including for the small joints of the hands and feet (De Jong et al., 2004).

For any arthritis exercise programme, the key point is to identify an exercise regimen that best meets an individual's needs and expectations. It needs to be safe, effective, and personally pleasurable (Wing & Peterson, 2012). It has been suggested that a trial of any complex intervention should include a description of the intervention and its components as an essential step of reporting (Craig et al., 2008; Medical Research Council, 2000).

Complex interventions are usually described as interventions that contain numerous interacting components (Craig et al., 2008). However, other important points to be taken into account are the number and variability of outcome measures; number of groups or organisational levels targeted by the intervention; degree of flexibility or tailoring of the intervention permitted and the number of interacting components within the experimental and control interventions (Craig et al., 2008).

In accordance with the principles of the Medical Research Council (MRC), framework guidance for complex interventions exercise protocols for each treatment arm should be founded on evidence-based knowledge acquired through treatment modality-specific training courses, peer-reviewed best practice and

clinical experience (Campbell et al., 2007; Craig et al., 2008; Medical Research Council, 2000). Therefore, a description of the intervention and its components should be included in any trial of complex intervention as an essential step of reporting (Heine et al., 2012; Medical Research Council, 2000). A pragmatic approach was taken to reporting the treatment of patients.

A large and growing body of systematic reviews of the literature has started to establish the evidence base for exercise in RA. This has involved a general exercise programme being designed for the whole body called ‘Whole Body Programmes’ (WBP) (Heine et al., 2012). Several studies investigating the effects of various types of exercise on different aspects of the patient experience have been carried out, the majority reporting beneficial responses (Van den Ende et al., 2007; Van den Ende et al., 2004). Almost all have involved WBPs that focus on aerobic fitness, strengthening and/or active range of movement. These programmes included all body joints such as small joints of hands and feet, large joint such as knee joints, elbows, ankle joints and shoulders. Exercise programmes from those studies that described the actual intervention in detail were also evaluated as part of designing the final RCT intervention protocol.

NICE guidelines (2009) recommend that all RA patients should have easy access to physiotherapists and occupational therapists for treatment of the condition. These treatments include joint protection advice, electrotherapy, exercise, assistive devices, splints, and heat and joint mobilisation (Beardmore, 2008; Heine et al., 2012). In order to prevent discrepancies, the treatment provided to all

participants was an intervention based on a combination of movement exercises, core stability, sustained stretching and balance exercises designed by the treating physiotherapists. Treatment was individualised for each patient according to the patient's needs. The researcher devised a treatment strategy sheet (Appendix 11) to record the treatment in collaboration with the senior therapists who provided the treatment on each site.

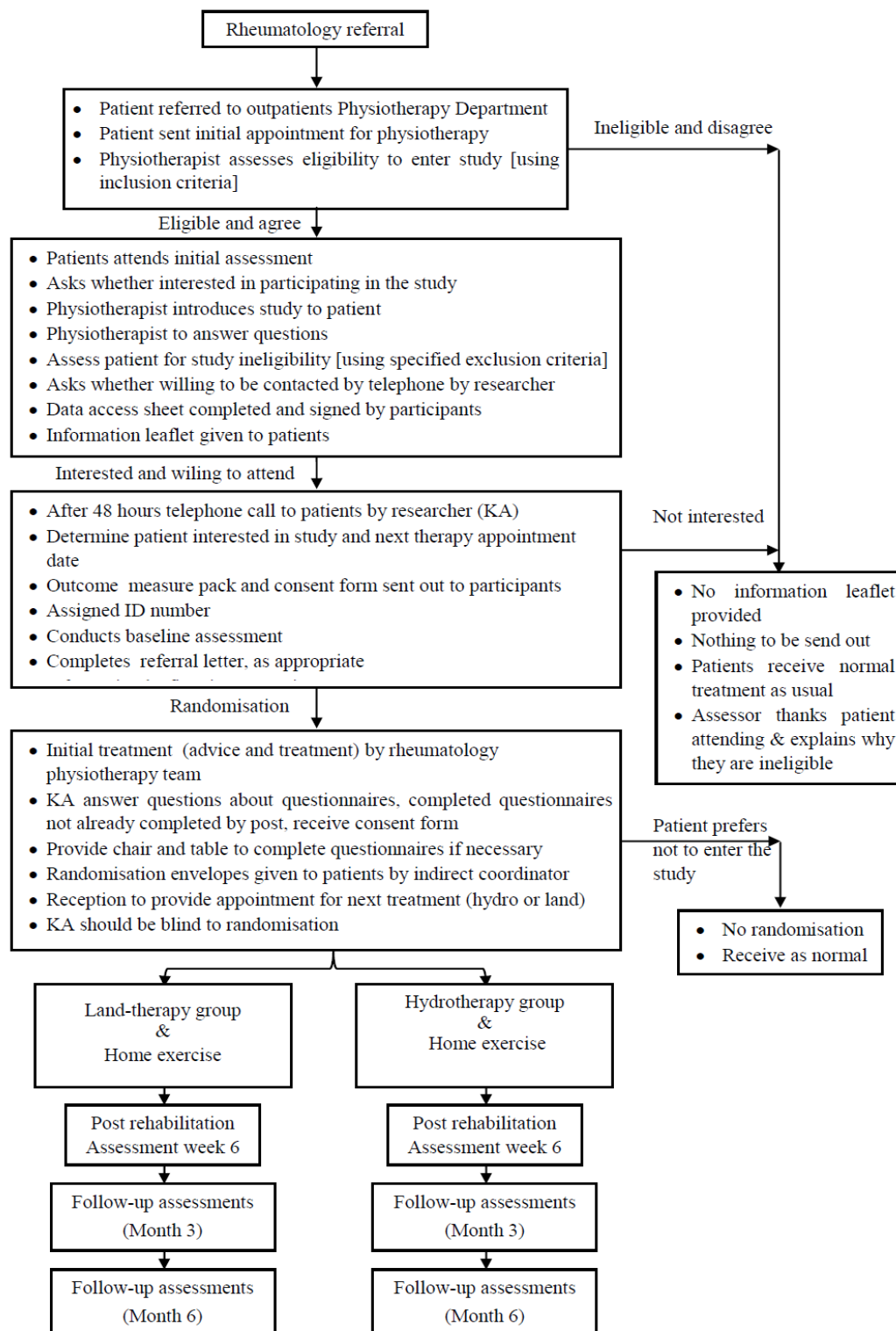


Figure 5.1: Flow diagram of participants' progress through RCT.

There were minor differences in the type of rehabilitation exercises depending on therapist's experiences, participants' condition, and goals. The treatment was recorded using treatment strategy sheets (Appendix 11). The aim of the form was:

- To accurately record the treatment received by patients for research purposes.
- To permit easy transfer of data onto a database by the researcher.
- To provide a quick and easy to complete record of the treatment provided for the clinician.

This form was not meant as a substitute for medical records.

Hydrotherapy group: Participants received a course of aquatic physiotherapy once a week for six weeks, each session lasting 45 minutes and taking place in water heated to between 34 and 36° Celsius (Becker, 2009; Eversden et al., 2007; Rintala et al., 1996). Because of the size of the therapy pools, each session included between two and four patients and was supervised by one therapist and one therapy assistant. The size of pool where the study was carried out was 7.4 m² in total (outer surface of the pool) (Figure 5.2, p.132) (Salford Royal Foundation NHS Trust, 2007).



Figure 5.2: Hydrotherapy pool, used with kind permission from WG (hydrotherapy lead within Salford Royal Foundation Trust).

There were three sections of the exercise hydrotherapy programme (Appendix 12). The first section, a warm up exercise lasting five minutes included such activities as walking, sidestepping, knee to chest walking, heel to bottom walking, hip abduction/adduction and flexion/extension. The second section was called the conditioning programme and consisted of a variety of movements in different positions (standing, sitting, supine) supported by hydrotherapy equipment such as floatation rings, fins, balls and woggles (Salford Royal Foundation NHS Trust, 2007). This section included sustained stretching exercises, range of movement, core stability exercises, balance exercises, proprioception and muscle strengthening exercises (Appendix 12). Finally, the cool down period (lasting five minutes) consisted of walking in the pool, side stepping, knee to chest walking/heel to bottom walking, hip abduction/adduction and flexion/extension.

The participants in this group also performed home exercises (twice daily x six weeks or until they reached their target) (Appendix 12). All patients in both groups performed the exercises tailored to their conditions and goals. The treatment protocols were led by the clinician to make them applicable to current national best practice and allow the protocol to be followed in the future within the framework of NHS budget constraints.

Land group: The land-therapy group exercises were undertaken once weekly for 45 minutes per session for six weeks in one-to-one sessions with the therapist while continuing with the HEP. The land exercise was part of the exercise rehabilitation programme (Appendix 13) (designed for arthritis patients and is used in SRFT) (Salford Royal Foundation NHS Trust, 2007). In addition, participants performed their HEP (twice daily for six weeks or until participants reached their target) (Appendix 13). The type of movements in the land exercise programme were almost identical for all RA patients in that group. They included a range of exercises such as those that worked on stretching, strengthening and core stability (Appendix 13). The intensity level was also initially issued on a case-by-case basis in respect of the individual's ability, after which it could be gradually increased if necessary. The exercise programme was devised by Salford Royal Foundation NHS Trust, 2007 and all patients in both groups performed their exercise programme regularly.

All participants were provided with a booklet containing pictures and advice about an exercise, describing the programme and resistance material required. Between

clinic sessions, all RA patients in both groups were also asked to perform the HEP daily. Moreover, patients in both groups were provided with a diary booklet during the first appointment for use at each exercise session, in order to record the completion of the exercise programme daily and every subsequent day until the next session.

5.2.3.1.4 Follow-up stage

The follow-up periods were three and six months. The researcher sent all the outcome measures to participants at three and six months.

5.2.3.2 Pilot study

Thirty-six patients were invited to take part in a pilot study to test the proposed protocol and increase the quality and internal validity of the study (Nyatanga, 2005; Van Teijlingen & Hundley, 2002). Initially, it was planned to recruit 10 participants for the pilot study; however, the hydrotherapy pool closed unexpectedly for refurbishment and recruitment stopped. Six patients were recruited to the pilot and 30 patients were not interested or excluded for the following reasons:

- Not all RA patients wanted to be part of the study because they wanted to be guaranteed to receive hydrotherapy without randomisation.
- Some were not appropriate for the study and did not fit the inclusion criteria.
- Not all RA patients wanted to have hydrotherapy either because of fear of water or because of work commitments.

- Not all RA referrals who were referred to the physiotherapy department required hydrotherapy; some needed, for example, only wrist splint and neck brace.
- They had commitments with other research studies.

After the pilot study, a new site was found and the protocol was amended to change the lower age limit to ≥ 18 years, and the following exclusion criteria were removed to reflect that of the department:

- Patients treated with intra-articular corticosteroid injection or physiotherapy treatment within four weeks of assessment were to be excluded to avoid overload effect on joint function.
- Any patients who had surgery in the three months prior to study entry or those who had surgery planned were excluded.

5.2.4 Outcome measures

RA is a chronic inflammatory disease associated with highly variable features of presentation and disease trajectory both within and between individuals (Van Riel & Van Gestel, 2000). Thus in the past, mainly in clinical trials, a huge number of outcome variables have been used because of this variety in disease expression (Van Riel & Van Gestel, 2000).

Boers et al. (1994) stated that the World Health Organisation (WHO) and the International League against Rheumatism (ILAR) had a core set of eight endpoints for RA. At least one of these endpoints had to be among this study's

main outcome measures. WHO/ILAR core set of endpoints for RA clinical trials included the following:

1. Pain was assessed using a 10cm VAS or Likert scale (Langley & Sheppeard, 1984).
2. Patient global assessment was examined using AIMS or Likert scale (Meenan et al., 1980).
3. Physical disability or physical functioning was examined using the Stanford Health Assessment Questionnaire (Fries et al., 1982), AIMS (Meenan et al., 1980), McMaster Health Index Questionnaire (MHIQ) (Chambers et al., 1982) or McMaster Toronto Arthritis Patient Preference Questionnaire (MACTAR) (Tugwell et al., 1987).
4. Swollen joints (Ritchie et al., 1968).
5. Tender joints (Ritchie et al., 1968).
6. Acute phase reactants (Felson et al., 1993).
7. Physician global assessment using VAS or Likert scale.
8. Radiographs of joints (in studies lasting more than one-year).

To assess outcome measures in RA a wide range of measures may be used in terms of patient perspective (functional status, health status and health-related QoL) (Hakala, 1997; Pincus, 1995). All the outcome measures used in this study were patient self-reported, except DAS28, which was completed by the clinicians. The psychometric properties of these questionnaires are well established (Fitzpatrick et al., 1992). HAQ was used to measure physical function (functional ability, pain and GWB) using HAQ-DI, HAQ_{VAS} and HAQ-GWB respectively;

DAS28 and RADAI measured disease activity through clinician assessment and the completion of a self-administered questionnaire respectively; EQ-5D tariff and EQ-5D_{VAS} was used to measure HRQoL and health status; hospital anxiety depression scale (HADS), hospital anxiety depression-depression scale (HAD-D), hospital anxiety depression-anxiety scale (HAD-A) was used to measure psychological wellbeing and mood changes in terms of anxiety and/or depression.

All the outcome measures were assessed at baseline within one week (before intervention), six weeks post-intervention (within one week, post-treatment), three months (after baseline) and six months follow-up (after baseline). The assessment was completed when questionnaires which had been distributed by the researcher at a set time point were returned.

The primary end points were placed at six weeks to reflect clinical practice in the HYDAT team (2009) and other hydrotherapy studies. When checking for follow up periods some of the hydrotherapy studies only followed up their participants for three months (Eversden et al., 2007; Hall et al., 1996) whereas Bilberg et al. (2005) followed only the hydrotherapy group for six months. In order to further strengthen the veracity of the study, there were two periods of follow up.

5.2.4.1 Physical function measurement

The most important category of outcome in arthritis might well be disability (Boers et al., 1994; Fries et al., 1980; Fries, 1983). In RA, disability is a common outcome and has a major impact on daily life, as well as socioeconomic

consequences (Boers et al., 1994; Fries et al., 1980). The level of disability has a significant impact on patients and society in terms of the financial and social costs of the disease (Boers et al., 1994; Fries et al., 1980; Fries, 1983). There are different instruments for assessing disability in RA, but the most widely used are self-reported questionnaires (Lillegraven & Kvien, 2007). One of the most widely used disease-specific arthritis tools is the HAQ-DI which was used (ARAMIS, 2009; Bruce & Fries, 2005; Felson et al., 1993; Fries et al., 1980). The two most frequently used questionnaires in arthritis are HAQ (ARAMIS, 2009; Fries et al., 1982) and AIMS (Meenan et al., 1980).

Many other instruments were developed to be used in RA, but only HAQ and AIMS offer the possibility to assess their potential value and have a sufficiently validated widespread focus (Fitzpatrick, 1996). Other older scales, on the other hand, tend to be fairly limited and insensitive to functional disability (Bowling, 2003). Since disability in RA is multidimensional, other versions have been developed, such as the modified-HAQ (Pincus et al., 1983) and the multidimensional HAQ with more items (Anderson et al., 2010; Pincus et al., 1999), but these are less commonly used in clinical trials and in daily practice.

Fries et al. (1980) developed the HAQ in 1978. The HAQ was among the first instruments to have been based on generic, patient-centred dimensions for measurement of physical function (Fries et al., 1980), and use of this questionnaire is now indicated in most RA clinical trials (ARAMIS, 2009; Bruce & Fries, 2005; Fries et al., 1980) and it is regarded as the gold standard outcome

measure for assessing functional status (Bruce & Fries, 2005). Sensitive to change of functioning status, even over short time intervals, HAQ is authorised and recommended by the ACR. It is available in more than 60 languages and is supported by a bibliography of more than 500 references (ARAMIS, 2009; Bruce & Fries, 2005).

The HAQ is originally designed as a disease-specific questionnaire. However, it has been developed and successfully applied for assessing functional disability in a variety of rheumatic diseases (Bruce & Fries, 2005; Ramey et al., 1992). HAQ can be administered in diverse disciplines and, with properly designed adaptations, in different cultures without any impact on its reliability or validity (ARAMIS, 2009; Bruce & Fries, 2005).

There are two versions of HAQ: full HAQ and short HAQ (2-pages HAQ) (Bruce & Fries, 2005). The full HAQ assesses the dimensions of postponing death, avoiding disability, drug side effects, discomfort and pain, and economic costs, while the short HAQ is comprised of the HAQ disability index (HAQ-DI) and the HAQ patient global health status and pain VAS (Bruce & Fries, 2005). The difference between full HAQ and short HAQ is that the items in the short HAQ remain constant, while in the full HAQ, items like drug side effects and costs as well as supplemental sections on demographics, lifestyle and costs are periodically tailored to uncover specific hypotheses or research questions to capture the long-term impact of chronic illness (Bruce & Fries, 2005).

HAQ-DI (Appendix 5)

The HAQ-disability index (HAQ-DI) is used in this study as the primary outcome measure and consists of eight weighted categories that are designed to measure a person's ability to dress, arise from a chair or bed, eat, walk, perform basic toileting (hygiene), reach, grip, and perform normal activities. Sexual activity was included in an earlier version (Bowling, 2004) but was removed after a reluctance to report this (Fries et al., 1980). Each category is scored on a 4-point scale (Bruce & Fries, 2005; Bruce & Fries, 2003).

- 0 = Is able to perform the activity without any assistance.
- 1 = Is performing the activity with some difficulty.
- 2 = Is performing the activity with great difficulty (needs assistance of others to perform the specific activity).
- 3 = Unable to do the task (cannot perform the specific activity).

Interpretation of the test result may be classified as follows (Bruce & Fries, 2003):

- 0.00 to 1.00 mild to moderate difficulty or disability.
- 1.01 to 2.00 moderate to severe difficulty or disability.
- 2.01 to 3.00 severe to very severe difficulty and disability; dependence on others.

Thus, a high HAQ indicates loss of functional capacity – so the lower the HAQ score, the better the functional status (Bruce & Fries, 2003).

Advantages of HAQ-DI

We chose the HAQ-DI as the primary outcome measure because functional limitation is an important factor in RA patients, which can be easily measured by the HAQ-DI. Functional disability is one of the main outcomes in a core set of eight endpoints for RA (Boers et al., 1994). Disability is a common outcome in RA and has an impact on daily life as well as socio-economic consequences. More than one third of working people are no longer able to work five years after the onset of the disease, indicating the consequence of the disease on working status (Scott et al., 2003; Scott et al., 2000).

HAQ-DI rather than AIMS was chosen for this study for the following reasons:

- The HAQ-DI is regarded as a self-administered questionnaire completed in five minutes and scored in less than one minute.
- It can be administered face-to-face (ARAMIS, 2009; Bruce & Fries, 2005) or in a telephone interview and it has been validated for both.
- The questionnaire can also be emailed to patients (ARAMIS, 2009; Bruce & Fries, 2005).
- HAQ-DI is a good measure of function and it was used extensively among clinicians in USA, UK and Europe (Bruce & Fries, 2005; Ramey et al., 1992).
- HAQ-DI is regarded as concise, reliable, valid, sensitive to change and can be either self-administered or interviewer-administered. It is also suitable for use in the community (ARAMIS, 2009; Bruce & Fries, 2003).

- AIMS covers physical, social and emotional wellbeing. However, it was not used in this study because the emotional wellbeing was evaluated in a separate questionnaire (HADS).
- HAQ-DI is designed to evaluate a patient's level of functional ability by including questions about activities involving both upper and lower extremities, also with fine movements (Bruce & Fries, 2003).

Moreover, the main reasons to investigate predictors for HAQ-DI are as follows:

1. To recognise the factors that predicts a poor outcome as early as possible in order to treat patients showing such characteristics more aggressively (Jansen et al., 2000). This approach may help to prevent joint damage and preserve functional capacity.
2. To test whether the various disease parameters correlate with the functional status.
3. This study first used the univariate analysis to explore which factors are independently predicting functional disability in patients with RA.

Reliability and validity of the HAQ-DI

The HAQ-DI is sensitive to change and is a good predictor of prospective disability and costs (ARAMIS, 2009; Michaud et al., 2003; Wolfe & Zwillich, 1998). It has had verified reliability and validity in different languages and contexts (ARAMIS, 2009). Literally hundreds of studies have demonstrated its validity (ARAMIS, 2009; Bruce & Fries, 2005). There is an agreement that the HAQ-DI has face and content validity (ARAMIS, 2009; Bruce & Fries, 2005;

Ramey et al., 1992). Correlations between the questionnaire or interview scores and task performance ranged from $r = 0.71$ to 0.95 demonstrating criterion validity among RA patients (ARAMIS, 2009; Bruce & Fries, 2005).

HAQ-DI scoring

A large and growing body of HAQ-DI literature has confirmed and emphasised that when there are scores for less than six of the eight categories, the score cannot be validly calculated (ARAMIS, 2009; Bruce & Fries, 2005). The Standard way of scoring takes into account the use of aids/devices. Three steps are needed for calculating HAQ-DI overall score (with aids/devices):

1. Each category contains at least two specific subcategory questions; the highest subcategory score determines the value for each category, unless aids or devices are used.
2. Adjust the score if there is any use of aids/devices and/or help from another person.
3. To obtain a HAQ-DI score of 0-3, the sum of category scores is divided by the number of categories answered (zero = best-, three = worst-functioning). There must be responses in at least 6 of the 8 categories or else a HAQ-DI cannot be computed.

HAQ_{VAS} (pain score) (Appendix 5)

The measurement of pain is an essential dimension in patients with RA. HAQ_{VAS} a double-anchored VAS was designed to obtain data relative to the presence or absence of arthritis-related pain and its severity (Bruce & Fries, 2003; Bruce &

Fries, 2005). This scale measures pain on a horizontal VAS with “no pain” at one end (scored 0) and “severe pain” at the other (scored 100) (ARAMIS, 2009; Bruce & Fries, 2003; Bruce & Fries, 2005; Fries et al., 1982). The goal is to obtain information from patients on how their pain has tended to be over the past week, although it is understood that pain may be reported to have diverged over the course of a day or from day to day (ARAMIS, 2009; Bruce & Fries, 2003; Bruce & Fries, 2005).

The VAS line is standardised to 15 centimetres in length. To indicate the severity of their pain, patients are instructed to place a vertical mark on the line (ARAMIS, 2009; Bruce & Fries, 2005).

$$\frac{A = \text{Score of patient}}{B = \text{VAS Length}} \times \frac{?}{100}$$

If a patient reports a percentage, multiply the percentage by three. Use the midpoint if a patient puts more than one mark. If a patient points a horizontal line below the pain scale, and not a vertical one, the midpoint of that line is taken. If the line starts at the beginning of the scale, measure to the end of the line, not the middle.

Calculating the pain score: Measure the distance in centimetres and multiply by 0.2; this provides a score from 0 to 3. For example, if the mark is at 5cm, 5 x 0.2 yields a pain score of 1.0.

Pain was used as a secondary outcome measure for the following reasons:

- Pain is one of the most prominent symptoms in the majority of people with RA (McKenna & Wright, 1985; Walsh & McWilliams, 2012).
- Pain is a common purpose for primary care consultation (Uhlig et al., 2002).
- Pain is a major cause for increased health care costs (Crook et al., 1984).
- Previous studies have included pain as an outcome to measure the effects of hydrotherapy for patients with RA (Rintala et al., 1996).
- Pain is one of the core set of eight endpoints for RA (Boers et al., 1994).
- Pain is easy to score without being a burden to the patient (Huskisson, 1974).
- VAS is regarded as a reliable and valid measure of pain, primarily when comparing individuals over time for three to four times (Huskisson, 1974).

HAQ-GWB (Wellbeing score) (Appendix 5)

The scale that measures GWB is on a horizontal scale with “very well” at one end (scored 0) and “very poor” at the other (scored 100). GWB was used as a secondary outcome measure for the following reasons:

- RA imposes an immense burden on the individual's ability to cope, and may greatly diminish QoL and psychological wellbeing (Fitzpatrick et al., 1988).
- It incorporates a VAS, which is easy to score and is without burden to the patient (Huskisson, 1974).

5.2.4.2 Health-related quality of life (HRQoL) measurement

QoL is the awareness of a person's position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns (WHOQOL group, 1995). Across a wide spectrum of diseases and conditions, there has been an upsurge of interest in the development of a generic instrument that can be used to measure HRQoL (Hawthorne, et al., 2000; Hurst et al., 1997; Hurst et al., 1994; Rabin et al., 2011a). These generic questionnaires have advantageous outcomes and, besides just the beneficial and detrimental effect of medication on the individual, capture the overall impact of disease (Cheung et al., 2009; Hawthorne, et al., 2000; Hurst et al., 1997; Rabin et al., 2011a).

Health status profiles characteristically measure an individual's health status across different dimensions, to reflect their HRQoL. In Study One, generic measures of HRQoL were measured by using EQ-5D (Brooks, 1996; Cheung et al., 2009; Hurst et al., 1997; Rabin et al., 2011a). There are other well-validated, popular, generic health-related QoL scales (also called health-status scales) that have been used to assess outcomes in rheumatology such as the SF-36 (Ware, 1993; Ware & Sherbourne, 1992), the Nottingham Health Profile (NHP) (Hunt et al., 1985), the Sickness Impact Profile (SIP) (Bergner et al., 1976), the Quality of Wellbeing Scale (QWB) (Balaban et al., 1986), the Functional Status Questionnaire (FSQ) (Jette et al., 1986) and the Framer Quality of Life Scale (Rudick et al., 1992).

De Jong et al. (1997) developed a specific questionnaire called RA quality of life (RAQoL). This instrument is used to measure pain and fatigue in addition to other disease specific issues (De Jong et al., 1997). This instrument has been found to have excellent test-retest reliability, good internal consistency and good content validity; however, the main difference between the RAQoL and others is that it uses a qualitative approach and lengthy interviews (De Jong et al., 1997). It has been recommended that QoL should be assessed using questionnaires rather than interviews (Berndtsen et al., 1994; Guyatt et al., 1993).

EQ-5D

EQ-5D is a validated generic QoL instrument developed by the EuroQol Group (Hawthorne, et al., 2000; Rabin et al., 2011a). EQ-5D is a generic, simple measure of health for clinical and economic appraisal of healthcare. It consists of two parts: a descriptive profile (EQ-5D tariff) for measuring economic health (Appendix 6) and a VAS (EQ-5D_{VAS}) (Appendix 7) for measuring health status (Drummond et al., 2005; EuroQol Group, 1990). EQ-5D essentially consists of two parts: the EQ-5D descriptive system called EQ-5D 3L or called EQ-5D tariff. The EQ-5D visual analogue scale (EQ-5D_{VAS}) (Hawthorne, et al., 2000; Rabin et al., 2011a). Costs per quality-adjusted life year (QALY) were derived from health states measured for economic health (Drummond et al., 1997; Drummond et al., 2005; EuroQol Group, 1990). EQ-5D is a self-administered questionnaire easily completed by respondents without the need for support or help within a few minutes (Hurst et al., 1997; Rabin et al., 2011a).

EQ-5D tariff (Appendix 6)

The subjects report their level of ability on that day depending on five items; each item includes three ordinal response levels; this is called EQ-5D-3L. The five categories are namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each category has three levels: no problems, some problems, severe problems. This decision results in a single-digit number expressing the level selected for that dimension. The digits for five dimensions can be combined in a five-digit number describing the respondent's health state. It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score. These categories are coded to form a health profile, for example 11111 indicates no problems for any dimension, which therefore equals perfect health, while state 11223 indicates no problems with mobility or self-care, some problems with performing usual activities, moderate pain or discomfort and extreme anxiety or depression, and 33333 indicates extreme problems in every dimension, resulting in the worst imaginable health state possible (EuroQol Group, 1990; Rabin et al., 2011a). The health profiles classified them to one of 245 unique EQ-5D tariffs (or 'health states') ranging from one, indicating the best imaginable health state, and zero, representing death. Some health states attract negative values (to -0.594) indicating that from a societal perspective, these health states are regarded as worse than death (Hurst et al., 1997; Rabin et al., 2011a). Instructions to respondents are included in the questionnaire (EuroQol Group, 1990; Wolfe & Hawley, 1997). The EQ-5D has been used with patients with RA (Hurst et al., 1997), and there is evidence that it has moderate construct validity

(Spearman rho = .71) and reliability (ICC = .70) when used with patients (n = 82) with knee OA (Fransen & Edmonds, 1999).

EQ-5D_{VAS} (Appendix 7)

Records of the response has self-rated health on a vertical, VAS, where the endpoints are labelled ‘best imaginable health state’ and ‘worst imaginable health state’.

In Study One, the EQ-5D was used because it is widely accepted as an easy-to-use tool for measuring the relative cost-effectiveness of an intervention, while measuring health status at the same time (Hurst et al., 1997; Rabin et al., 2011a). The original intent in this study was to assess the CE of the two interventions in terms of cost per QALY gained.

HRQoL or QoL was used interchangeably within this thesis. It was used in secondary outcome measures for the following reasons:

- In RA patients, the assessment of HRQoL is relevant and is important in both clinical research and daily clinical practice (Hawthorne, et al., 2000; Kvien & Uhlig, 2005).
- Changes in HRQoL provide important information in RCTs & observational studies (Hawthorne, et al., 2000; Kvien & Uhlig, 2005).
- Priorities for resource allocation within the NHS were based increasingly on evidence of the CE of medical interventions on

HRQoL, providing further consideration (Hawthorne, et al., 2000; Hurst et al., 1997).

EQ-5D was chosen for this study rather than other outcome measures such as SF-36, NHP, and SIP because:

- The EQ-5D has been used with RA patients (Hurst et al., 1997).
- There is evidence that it has moderate construct validity (Spearman rho = 0.71) and reliability (intraclass correlation coefficient (ICC) = 0.70) when used with OA patients (n = 82) (Fransen and Edmonds, 1999).
- EQ-5D is quick, simple to use and easy to complete (Hawthorne, et al., 2000; Rabin et al., 2011a).
- It offers less complex health-state descriptors over the others and is more easily comprehended by patients (Hawthorne, et al., 2000; Hurst et al., 1997; Rabin et al., 2011a).
- SF-36, NHP and SIP are lengthy and time consuming. SF-36 functional ability scale concentrates mainly on mobility; therefore, it is unlikely to be sufficiently sensitive as an outcome measure in rheumatology (Hurst et al., 1997).
- The reliability of the EQ-5D index and EQ-5D_{VAS} is better than all other instruments except the HAQ, and is sufficiently reliable for group comparisons (Hurst et al., 1997).

- It is responsive to change and therefore valid as an outcome measure in clinical trials, audit and health economic studies (Drummond et al., 2005; Hawthorne, et al., 2000).

An updated version of the EQ-5D, called the 'EQ-5D-5L', was published in 2011 (Rabin et al., 2011b). It includes the five dimensions, but each dimension has five response levels rather than three (Rabin et al., 2011b). EQ-5D-5L was designed in order to potentially reduce ceiling effects, maintain feasibility and significantly improve reliability and sensitivity (discriminatory power) (Rabin et al., 2011b). It has been validated for arthritis but its reliability and responsiveness has not yet been demonstrated (Rabin et al., 2011b).

5.2.4.3 Disease activity measurement

Disease activity is an important factor – both in clinical care and in the research domain – in the evaluation and assessment of patients with RA (Fransen et al., 2000). In rheumatic disease, quantitative assessment of patients differs from that of those with other chronic diseases, such as HT or hypercholesterolemia (Pincus, 2006), thus there is the need to assess different aspects of the underlying disease due to high variability of presentation and trajectory. Many comprehensive simple tools have been developed for the evaluation of disease activity in RA, including the Disease Activity Score (DAS) (Van der Heijde et al., 1990), the Disease Activity Score 28 (DAS28) (Prevoo et al., 1995), the Simplified Disease Activity Index (SDAI) (Aletaha & Smolen, 2005; Smolen et al., 2003) and the Clinical Disease Activity Index (CDAI) (Aletaha & Smolen, 2005). Three further self-

reporting questionnaires of disease activity are used in rheumatology, including the Rheumatoid Arthritis Disease Activity Index (RADAI) (Stucki et al., 1995), the Rapid Assessment of Disease Activity in Rheumatology (RADAR) (Mason et al., 1992) and Routine Assessment of Patient Index Data 3 (RAPID 3) (Pincus et al., 2008). Table 5.1 (p.158) provides a content summary of measures disease activity in RA (Fransen et al., 2003).

The SDAI and CDAI are two new tools for the evaluation of disease activity in RA. They have been developed to give both physicians and patients simple, optional instruments (Aletaha & Smolen, 2005). Nevertheless, these two options have not currently replaced the more frequently used instrument, DAS28 (Aletaha & Smolen, 2005). The CDAI is the only option that does not consider acute-phase response as a variable in the measurement, and it can be applied to conduct disease activity anytime and anywhere (Aletaha & Smolen, 2005). Patient self-reported measures are available in all these indices, which are defined as global health in DAS and DAS28, and referred to as ‘patient global assessment of disease activity’ in SDAI and CDAI (Aletaha & Smolen, 2005).

Disease activity measurement was used in secondary outcome measures for the following reasons:

- In RA, assessments of disease activity among rheumatologists have been shown to differ widely as shown by Kirwan et al. (1984). Many variables of disease activity are recorded to monitor the course of the disease in clinical practice and in clinical trials (Prevoo et al., 1995).

- Disease activity indices include a wide core set of eight endpoints for RA (Boers et al., 1994).
- Joint swelling, joint tenderness, and destruction of synovial joints are the main symptoms of RA, and are main items of disease activity associated with it (Aletaha et al., 2010). Both joint swelling and tenderness are part of DAS28 and RADAI.
- Disease activity is improved by early therapeutic intervention, which then reduces further joint damage and disability (Aletaha et al., 2010).
- The treatment strategies of RA patients are influenced by the responses given in the DAS (Aletaha et al., 2010).

The RADAI (Appendix 8)

RADAI is a disease-specific outcome measure developed to assess patient-reported disease activity in RA, and can be used as an alternative for, or complement to, the physician's assessments of disease activity (Fransen et al., 2003; Stucki et al., 1995). The DAS28 primarily consists of physician-assessed and laboratory-based variables, while RADAI is a self-administered questionnaire combining five items into a single index (Stucki et al., 1995). It is a modification of the questionnaire introduced by Mason et al. (1992). Mason et al. found that there was a high consensus between patients and physicians in terms of scoring the RADAR questionnaire (Mason et al., 1992).

The RADAI is a five-item questionnaire which includes: (1) global disease activity in the last six months, (2) disease activity in terms of current swollen and

tender joints, (3) arthritis pain, (4) the duration of MS and (5) tender joints to be rated in a joint list (Fransen et al., 2003; Stucki et al., 1995). The first three items are all rated on an anchored Numerical Rating Scale (NRS) from zero to 10, where higher scores indicate more disease activity (Fransen et al., 2003; Stucki et al., 1995). The scores on the last two items range from zero to six and zero to 48, respectively, but are transformed on the same scale of zero to 10.

Validity and reliability of RADAI

The RADAI has been shown to have adequate reliability, validity and responsiveness among Swiss patients with RA (Mason et al., 1992), and is a feasible and valid instrument completed easily by patients (Fransen et al., 2000).

The internal consistency and validity of the RADAI is high for a questionnaire consisting of only five items (Fransen et al., 2000; Nunnally & Bernstein, 1994). Cronbach's Alphas of 0.91 and 0.87 have been recorded (Fransen et al., 2000; Stucki et al., 1995). The association between internal consistency and RADAI items support the summation of item scores into total score (Fransen et al., 2000). Joint counts are the principal category used in most studies on reliability and validity to indicate patients' perception of sign and symptoms (Fransen et al., 2000).

It has been shown that the joint count was reliable in several studies (Prevoo et al., 1996; Stewart et al., 1990; Taal et al., 1998). Stucki et al. (1995) assessed test and retest reliability of joints listed in RADAI, and confirmed Kappa values ranging from $r = 0.52$ to 0.72 in different joints. For pain, global disease activity and MS,

there was good test-retest reliability found by Hanley et al. (1996) with ICC ranging from $r = 0.81$ to 0.85 . Test-retest reliability of RADAI was very high (ICC 0.92) (Fransen et al., 2003). For convergent validity, the RADAI scores were correlated with the DAS28 ($r = 0.53$), the HAQ ($r = 0.56$), the correlation of RADAI with ESR was low ($r = 0.27$) (Fransen et al., 2003; Fransen et al., 2000). For responsiveness to change, the RADAI score was changed from mean 4.5 to 2.9 ($P < 0.0001$) (Fransen et al., 2001). The RADAI and DAS28 were equally sensitive in detecting a flare (predictive ability 0.88) and had equal size effect (Fransen et al., 2001; Fransen et al., 2003).

The DAS28 (Appendix 9)

DAS28 is a measure of disease activity in RA, which has been shown to be a valid estimator of disease activity (Van Riel et al., 2001). Since the DAS28 contains summary joint counts, it is practical to use for monitoring RA disease activity in clinical practice (Fransen et al., 2003; Felson et al., 1998).

The DAS is calculated by a complex mathematical formula from results of 28 swollen joint counts and 28 tender joint counts (TJCs) and ESR; these will have already been taken in the clinic, and reflect the blood marker for inflammation and sometimes a general health assessment on a visual analogue (Felson et al., 1998; Fransen et al., 2003). The DAS28 can also be calculated using C-reactive protein (CRP) instead of ESR (Fransen et al., 2003). ESR ranges from 0 to 150 , General Health ranges from 0 to 100 , and the range of the DAS28 is $(0 - 9.4)$ (Fransen et al., 2003). The DAS28 is easy and quick to administer and gives an internationally

acceptable objective assessment of disease activity that compares well with ACR criteria (Fransen et al., 2003; Prevoo et al., 1995).

For score interpretation (Fransen et al., 2003), the level of RA disease activity can be interpreted as:

- Low ($\text{DAS28} \leq 3.2$).
- Moderate ($3.2 < \text{DAS28} \leq 5.1$).
- High disease activity ($\text{DAS28} > 5.1$).

A $\text{DAS28} < 2.6$ corresponds with being in remission, according to the ARA criteria. The EULAR response criteria classify patients as good, moderate, or non-responders (Van Gestel et al., 1998). For example, a patient must show a significant change as well as low disease activity to be classified as a good responder (Fransen et al., 2003). The DAS28 is most easily calculated using a programmed calculator (online and downloadable calculators) and takes one minute.

The following formulas are used (Fransen et al., 2003; Prevoo et al., 1995):

$\text{DAS28-4 (four variables)} = 0.56 \times \sqrt{28\text{TJC}} + 0.28 \times \sqrt{28\text{SJC}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}.$

$\text{DAS28-3 (three variables)} = (0.56 \times \sqrt{28\text{TJC}} + 0.28 \times \sqrt{28\text{SJC}} + 0.70 \times \ln(\text{ESR}) \times 1.08 + 0.16.$

Reliability: Test-retest

Reproducibility of the DAS was determined by an inter-period correlation matrix of RA patients with ≥ 3 year's follow-up (Fransen et al., 2003).

Validity

For content validity, the DAS28 contains measures from the core set of eight points in assessment of RA efficacy after medications (Fransen et al., 2003). The DAS28 showed a high predictive ability ($ICC = 0.88$) in detecting a flare of RA disease activity (Fransen et al., 2001).

Table 5.1: Summary of content of measures of disease activity in RA (adapted from Fransen et al., 2003) and reproduced with permission of John Wiley & Sons, Inc.

Measure / Scale	Content	Assessment	Blood sample	Joint count	General health	Global disease activity	Pain	Morning stiffness	Functional status
DAS	Disease Activity Score (consisting of 44-tender joint count (TJC44), 44-swollen joint count (SJC44), acute phase reactant (ESR) and general health	Physician & patient	+	+	+	+			
DAS28	Disease Activity Score 28 (consisting of 28- tender joint count (TJC28), 28-swollen joint count (SJC28), acute phase reactant (ESR) and general health	Physician & patient	+	+	+	+			
RADAR	Rapid Assessment of Disease Activity in Rheumatology (consisting of current and past disease activity, pain, morning stiffness, functional status and a tender joint list)	Patient		+		+	+	+	+
RADAI	RA disease activity index (consisting of current and past disease activity, pain, morning stiffness and a tender joint list)	Patient		+		+	+	+	

5.2.4.4 Anxiety and depression measurement

Depression and anxiety are a part of psychological wellbeing assessment (Creed & Ash, 1992). These are the main psychiatric disorders reported in patients with RA, for example, phobia, stress, anxiety and depression (Isik et al., 2007; VanDyke et al., 2004). RA is a chronic systemic disabling disease with joint deformity, which leads to harmful psychological consequences because of pain, inability to work, functional limitations, and frequent hospitalisation (Mella et al., 2010). All these factors contribute to psychosocial and psychiatric symptoms such as depression and anxiety (Mella et al., 2010).

In RA the prevalence of depressive symptoms shows according to the screening methods used, clinical assessments and the samples studied results to be varied from 13%–20% and above (Covic et al., 2012; Dickens et al., 2002). Similarly, recent studies (El-Miedany & Rasheed, 2002; Isik et al., 2007; Söderlin et al., 2000) have reported giving varying prevalence rates of anxiety in the wide range of 21–70% due to differences between study samples or instruments used (Covic et al., 2012; Uguz et al., 2009). A higher prevalence of anxiety rather than depression was reported in some studies (El-Miedany & Rasheed, 2002; Ødegård et al., 2007), but not in others (Isik et al., 2007; Uguz et al., 2009). It is for these reasons that this outcome has been included in this study.

Previous studies have reported that a low education level (EL), increased disease duration (DD), morning stiffness (MS), rheumatoid factor (RF) and disease activity parameters are associated with psychiatric symptoms such as depression and anxiety (Covic et al., 2012; Katz & Yelin, 1993; Mella et al., 2010; Sheehy et

al., 2006; Wolfe & Michaud, 2009). It seemed intuitive therefore, to explore the relationship between psychological wellbeing (depression and anxiety) and socio-demographic characteristics, disease activity, in terms of a self-administered questionnaire (RADAI) or physician assessed questionnaire (DAS28).

The most commonly used scales for screening anxiety and/or depression in patients with RA include the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Hospital Anxiety Depression scale (HAD scale) (Zigmond & Snaith, 1983). This study chose the HADs as its tool because it has been extensively validated across various somatic and psychiatric populations, both in primary care and in the community (Bjelland et al., 2002; Covic et al., 2012).

The main difference between HAD and BDI is that, rather than correlating with RA activity, BDI depends on somatic items in which the scores correlate well with the depression score only (Bishop et al., 1987), whereas HAD specifically excludes somatic items to avoid an overestimation of emotional symptoms, which are frequent in physically ill patients (Mella et al., 2010; Zigmond & Snaith, 1983). Thus, this scale attempts to reduce bias caused by somatic complaints from the patients with RA.

The HAD scale (Appendix 10)

The HAD is a self-assessment mood scale specifically designed for use in non-psychiatric patients (Zigmond & Snaith, 1983). It is used to assess the presence of mood disorder, especially anxiety and depression (Zigmond & Snaith, 1983).

The HAD contains 14 items (seven items for anxiety and seven for depression) and takes two to five minutes to complete; for each item, there is a four-level response scored from 0-3 with a possible overall score ranging from 0 to 21 (Zigmond & Snaith, 1983). The depression subscale scores of 7 or less indicate normal cases, while scores of 8-10 in each subscale indicate probable cases, and scores of 11 or more indicate definite cases; this is the same for the anxiety subscale (Zigmond & Snaith, 1983). It means a score over 7 in each subscale is suggestive of anxiety or depression (Bjelland et al., 2002; Snaith, 2003; Zigmond & Snaith, 1983).

The presence of psychiatric disorders in RA patients could compromise the efficacy of treatment and may expedite disease progression (Young, 1992). In contrast, the success of RA treatment has been shown to increase with the improvement of psychiatric disorders (Parker et al., 1995; Sharpe et al., 2001). For those patients with clinically significant anxiety and depression, HADs is indicated as a reliable instrument (Zigmond & Snaith, 1983). HADs is easy to use and therefore widely used in the assessment of many chronic conditions (Bjelland et al., 2002; Herrmann, 1997). It is considered to be a valid measure of the severity of mood disorder, and will provide physicians with useful information about disease progression (Covic et al., 2009; Covic et al., 2012; Zigmond & Snaith, 1983).

5.2.5 Ethical application

The Ethics Committees of Manchester Metropolitan University (Appendix 14) and North West NHS 2 Research Ethics Committee-Liverpool Central approved

this study (Appendix 15). Other approval was obtained from research and development offices in each trust in CMFT (Appendix 16) and SRFT (Appendix 17).

5.2.6 Amendments

The study was submitted to the Ethics Committee on four separate occasions. Each submission led to amendments. The first requested the addition of an interim analysis, but this was advised against by the statistician as being inappropriate (Appendix 18). The title of the study was changed, patient information was ratified and made more patient-friendly, and various additions were made. Management permission was required from each host organisation prior to the study. A copy of the original RA disease activity index (RADAI) questionnaire by Stucki was provided to the Ethics Committee.

A second submission was made in December 2010. Again title change was recommended by specialist rheumatologists to include all RA participants, not only those with early RA. Two further questionnaires were added: DAS28 (Prevoo et al., 1995) (Appendix 9) and The HAD (Appendix 10). The next submission in March 2011 reflected feedback from Research & Development at CMFT. These included more changes in contact details and patient information. Other modifications related to comparisons between participating patients and general RA patients in the Manchester area to establish the generalisation of the study. August 2011 the fourth submission was made. Changes had been made to the protocol to permit the inclusion of patients at the physiotherapists' discretion, and decided on an individual basis despite some non-adherence from patients. The

age range was extended to >18 with no upper limit. The reference criterion by which RA is diagnosed was expanded; acceptable diagnosis was made using the 2010 ACR/European League against Rheumatism classification criteria. This submission was finally accepted.

5.2.7 Sample size calculation

Prior to data collection, sample size estimation was performed in order to determine the sample size target for the study. This calculation was based on existing data (Bilberg et al., 2005) rather than an estimation of effective size. The primary outcome measure that was used for this calculation was HAQ-DI (Fries et al., 1980). A power calculation was performed (power 80% and $\alpha = 0.05$) based on two independent group comparisons, and using the HAQ-DI as the primary outcome measures (SD = 0.3, clinical worthwhile difference = 0.2) (Bilberg et al., 2005), suggested that 35 patients were required in each group. Assuming 20% dropout during the follow-up period, 43 patients were required in each group. The study was powered to detect a significant difference in the primary outcome only and that all secondary analyses were exploratory.

Power calculation formula:

$$N = (2 (\sigma^2) / \text{clinically worthwhile difference}^2) \times 7.8 \text{ (Rigby \& Vail, 1998).}$$

$$N = (2 (0.3)^2 / (0.2)^2) \times 7.8 = 35 \text{ patients were required in each group.}$$

Where N is the sample size, σ is the assumed SD for the group; the clinically worthwhile difference was based on data from Bilberg et al. (2005). 7.8 refers to the value given requiring a 0.80 chance to detect the difference at the 0.05 level of significance (two sided) as described by Rigby & Vail (1998). The study employed a statistician (JM) as an external monitor who confirmed the power

calculation (Appendix 18). This was to avoid patients receiving physiotherapy intervention if it was found to be ineffective at some point during the study, or the patients would continue treatment if it was appearing to be effective.

5.2.8 Randomisation

After recruitment, participants were assigned to one of two groups. Instructions were provided to each patient in a sealed opaque envelope provided by the receptionist. The participant was asked to keep this information from the researcher. The envelopes were pre-prepared by the DoS and delivered to the department. Appendix 19 presents the randomisation method using blocks of four. Block randomisation is a method used to ensure that the numbers of participants assigned to each group is equally distributed (Beller et al., 2002). Each possible permutation of groups A and B (A = land and B = hydrotherapy) in blocks of four was assigned a number. A random number sequence was used to choose a particular block, which in turn sets the sequence greater than the number of permuted blocks (Beller et al., 2002). This method can be used for assessing many outcomes or variables in one study (Ferrucci, et al., 2004; Kendall, 2003). A drawback of this method is that the numbers allocated to each group may not be well balanced enough for a small study (Beller et al., 2002), however a balanced number of participants were allocated to the hydrotherapy and land-therapy groups in this study.

5.2.9 Data analysis and statistical consideration

Data were analysed according to the principles of 'intention to treat'. All data were analysed using IBM SPSS Statistics 19 for Windows statistical software (Armonk, New York 10504-1722, USA).

5.2.9.1 Test of normality/descriptive statistics

The Shapiro-Wilks procedure (for samples < 50) was used in each test to investigate the null hypothesis that samples represented a normally distributed population of all outcome measures (Field, 2009) (Appendix 20).

The mean and standard deviation (SD) of normally distributed data were calculated and reported for both groups (Morgan et al., 2010). The median and interquartile range of non-normally distributed and ordinal variables were calculated and reported (Morgan et al., 2010).

5.2.9.2 Inferential statistics

Between-group comparisons

Comparisons between groups for normally distributed data were made using an independent-sample T-test (Leech et al., 2005; Munro, 2005). For non-normally distributed data, the Mann-Whitney U-test was used (Leech et al., 2005; Munro, 2005).

Within-group comparisons

For outcome measures and satisfying normality conditions, repeated measures Analysis of Variance (ANOVA) were used together with a Bonferroni post-hoc analysis. The Friedman test with Wilcoxon post hoc tests were used for non-normally distributed data (Leech et al., 2005; Munro, 2005). The Alpha threshold was set at 0.017 (0.05/3) (Field, 2009; Leech et al., 2005). It is necessary to emphasise here that the 6 month follow-up period (Test 4) was not included in the 'within group' differences because the number of participants recruited were very small (9 in land group, 10 in the hydrotherapy group).

Relationships between variables

The relationships between the variables of the study outcomes for the parametric data were investigated using Pearson's rank correlation coefficient. The relationships of the variables for the non-parametric data were investigated using Spearman's rank correlation coefficient (Morgan et al., 2010; Munro, 2005; Salkind, 2009). Values of ($r < 0.30$ = low; 0.30 to 0.60 = moderate; $r > 0.60$ = high) (Field, 2009; Terwee et al., 2007).

Predictive factors of HAQ-DI

Univariate and combined multiple regression analyses were performed with HAQ-DI as the 'dependent variable' to examine factors that contribute to functional disability in patients with RA (Field, 2009). Multiple regression analyses cause less chance of predicting relationships because of the overlapping of symptoms and interaction of variables. Therefore, this study first used the univariate analysis to explore which factors were independently predicting functional disability in patients with RA. The following variables were used as independent factors to explore predictors of functional ability measured by 'HAQ-DI': depression and anxiety HAD scores, GWB, RADAI and EQ-5D tariff. However, the following variables that were tested using both multiple and univariate regression analyses were identified as not being predictors of functional disability such as age, gender, EL, smoking, HT, BMI, DD, medication, marital status, DAS28, RF and EQ-5D VAS. Significance level was set at $p < 0.05$.

The next chapter demonstrates the results of the RCT Study One.

CHAPTER SIX: RESULTS OF STUDY ONE (RCT)

6.1 Introduction

The purpose of this Chapter is to report the results of the RCT Study One comparing the hydrotherapy group and the land-therapy group. The results will reflect the aims as outlined in chapter five, p.120-121:

Primary aim: The primary aim of the RCT Study One was to:

- Evaluate the difference in outcomes for RA patients when treated with hydrotherapy as opposed to land based therapy.

Secondary aims: The secondary aims of the RCT Study One were to:

- Identify and evaluate the differences in demographic factors between the hydrotherapy and land-therapy groups.
- Identify and understand the reasons for the difference in functional ability measured by HAQ-DI between those receiving hydrotherapy and those receiving land therapy.
- Evaluate whether or not the hydrotherapy could improve pain and GWB, HRQoL, disease activity and mood symptoms (depression and anxiety) more effectively than land therapy in patients with RA.
- Determine the association between variables measuring disease activity.
- Determine the association between variables measuring psychological status with socio-demographic features and disease activity indices.
- Determine which factors predict functional disability.

The intended goal of this study was to recruit 43 RA patients into each of the two treatment groups and follow them for three and six months. However, recruitment was terminated early in the CMFT site because a decision had been made to close their hydrotherapy facility for more than six months for refurbishment. Therefore, the recruitment was only six patients from the CMFT site. The results from these patients were used as a pilot study (section 5.2.3.2 Pilot study, p.134). Because of the closure of the CMFT recruitment site, the researcher relied solely on the SRFT site for recruitment to the study. From the SRFT site, 70 RA patients were invited to participate between August 2011 and July 2012; of these, 22 were not interested in participating in the study; reasons are shown in Figure 6.1 (p.169). At the end of planned study period, 48 participants were assessed and agreed to participate.

In this chapter, section 6.2 presents the number of participants and reasons for drop out, and goes on to describe the patient demographic in each group. Section 6.3 provides the inferential result of this RCT work. The primary outcome measure was compared firstly in separate tables. All secondary comparable outcome measures were conducted together in separate tables. Within appendices, the primary outcome measure of HAQ-DI was conducted in separate cells.

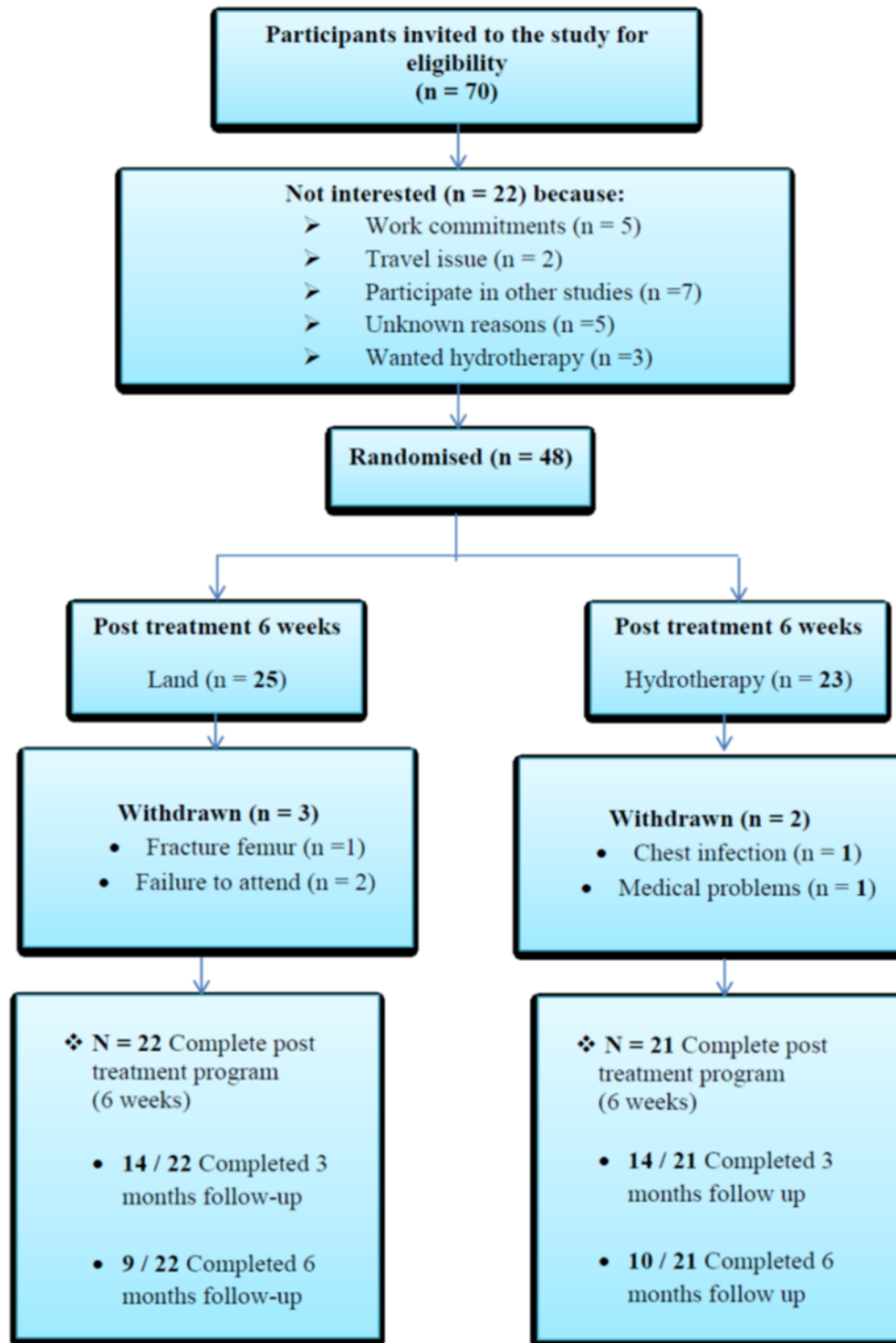


Figure 6.1: RCT study One outline.

6.2 Pilot results

Table 6.1 shows the reasons for incomplete sessions attended by participants as prescribed by the study protocol in both groups. Six participants (two men and four women) were randomised into two groups; two in the hydrotherapy group and four in the land-therapy group.

Table 6.1: Reasons for incomplete sessions of rehabilitation programme in pilot participants.

ID	Group	Number of sessions attended	Reason for incomplete sessions
CMFT 1	Land	2	Was in remission of disease activity and felt better
CMFT 2	Hydrotherapy	4	Had surgical knee replacement because of severe knee pain
CMFT 3	Land	3	Severe leg pain
CMFT 4	Hydrotherapy	6	Completed the programme
CMFT 5	Land	3	Had disease remission because of dramatic response to increase dose of C/S by physician
CMFT 6	land	3	Upper arm skin rash
Key: CMFT: Central Manchester Foundation Trust C/S: Corticosteroids			

Baseline characteristics of patients in the pilot study were comparable (Table 6.2, p.171).

Table 6.2: Characteristics at baseline of pilot participants.

Variables	Hydrotherapy group (n = 2)	Land group (n = 4)
Mean age (Years \pm SD)	(44 \pm 6. 4)	(55 \pm 21.5)
Age (min-max)	(40 - 49)	(25 - 72)
Gender (Females %)	100% (n = 2)	50% (n = 2)
Disease duration (Years \pm SD)	(11 \pm 5)	(10 \pm 7)
Occupation		
House wife	1	1
Retired	0	2
Unemployed	0	1
Employed	1	0
Medication		
NSAIDs	2	3
DMARDs	2	3
C/S	1	1
Biologics	1	1
RF	Positive (2) Negative (0)	Positive (2) Negative (2)
Anti-CCP	Positive (1) Negative (0) NR (1)	Positive (1) Negative (1) NR (2)
Mean height in cm	163	168
Mean weight in kg	66	77
Mean BMI	24	26
Primary outcome measure		
HAQ-DI[†] (overall score)	1.43 \pm 1	1.44 \pm 1.03
Secondary outcome measures		
HAQ_{VAS}[†] (Pain)	32 \pm 31	59 \pm 28
HAQ_{GWB}[†] (Wellbeing)	40 \pm 24	60 \pm 36
EQ-5D tariff[†] (QoL)	0.2 \pm 0.65	0.3 \pm 0.5
EQ-5D_{VAS}[†] (QoL)	51 \pm 15.5	46.2 \pm 32
RADAI[†] (Disease activity)	3.8 \pm 2.3	5.5 \pm 2.3
DAS28[†] (Disease activity)	6.5 \pm 1.2	4.6 \pm 1.1
HADS[†] (Mood change)	17 \pm 5.6	21 \pm 11.5
[†] Values are in mean (SD) and by independent t-test Key: HAQ-DI: overall score range from 0-3, with 0 being best functioning, and 3 worst functioning HAQ _{VAS} score (0-100), 0 being no pain, and 100 being severe pain HAQ _{GWB} scores (0-100), 0 being very well, and 100 being very poor EQ-5D tariff: scores range from -0.594-1, with 1 being perfect health, and -0.594 being worse than death EQ-5D _{VAS} : score range from 0-100, with 0 being low quality, and 100 being high quality RADAI: overall score range from 0-10, with 0 being no disease activity, and 10 being very severe DAS28: overall score range from 0-9.4, with 0 being no disease activity, and 9.4 being very severe HAD: overall score range from 0-42, with 0 being no depression and/or anxiety, and 42 being very severe depression and/or anxiety DD: disease duration Anti-CCP: anti-cyclic citrullinated peptide antibody (anti-citrullinated protein) RF: rheumatoid factor SD: standard deviation NR: not reported BMI: body mass index NSAIDs: non-steroidal anti-inflammatory drugs DMARDs: disease-modifying anti-rheumatic drugs C/S: cortico-steroids		

6.3. Randomised controlled trial (RCT) results (Study One)

Of the 48 potential participants that agreed to participate 2 out of 23, (8.6%) in the hydrotherapy group dropped out from the study after their initial agreement (one due to a chest infection and feeling that he/she could not spare the time for hydrotherapy treatment, another being unable to attend due to medical complications). Three participants out of 25 (12%) in the land-therapy group withdrew from the study after the first session (one because of an unrelated fractured femur, and the other two because they decided they were not interested in the study).

Finally, 43 participants (11 male, 32 female) completed post-treatment study at Test 2 (21 in hydrotherapy versus 22 in land therapy). 28 out of 43 completed three months' follow-up at Test 3 (14 in each group). 19 out of 43 completed six months follow-up at Test 4 (9 in land therapy versus 10 in hydrotherapy) (Figure 6.1, p. 169).

6.3.1 Patients' demographics

Table 6.3, p.173 displays the characteristics of those participants who entered the study at Test 1. The means (SD), medians (IQR) and percentages of Test 1 characteristics of patients in both exercise groups were comparable. However, most of these demographic data will be discussed in more depth in chapter 7, as part of comparisons with Study Two and other literature rheumatology studies.

Table 6.3: Characteristics of RCT patients at baseline.

Variables	Hydrotherapy (n = 21)	Land (n = 22)
Age (years)*	58 (14)	62 (16)
Age (range)	(29 – 74)	(23 – 82)
Gender (Females %)	71.4 %	77.3 %
Disease duration (Years)*	11 (12)	8 (6)
Occupation		
House wife	9.5 %	4.5 %
Retired	47.6 %	50 %
Unemployed	14.3 %	4.5 %
Employed	28.6 %	41 %
Medication		
NSAIDs (n)	67 % (14/21)	77 % (17/22)
DMARDs (n)	95 % (20/21)	77 % (17/22)
C/S (n)	24 % (5/21)	23 % (5/22)
Biologics (n)	14 % (3/21)	14 % (3/22)
Height in cm[†]	165 (10)	164 (10)
Weight in kg*	73 (20)	75 (20)
BMI*	27 (7)	27 (6)
Rheumatoid Factor		
+ ve	61.9 %	63.6 %
- ve	33.3 %	31.8 %
NR	4.8 %	4.6 %
Anti-CCP		
+ ve	19 %	4.5 %
- ve	19 %	36.4 %
NR	61.9 %	59.1 %
Smoking positive	11 %	13 %
Prevalence of depression	47 %	23 %
Prevalence of anxiety	38 %	23 %
Hypertension positive	28 %	31 %
[†] Values are in mean (SD) and by independent t-test *Values are in median (IQR) and by Mann-Whitney u-test Note: Prevalence of depression in all RA participants is 35%; prevalence of anxiety in all RA participants is 30% Key: Anti-CCP: anti-cyclic citrullinated peptide antibody (anti-citrullinated protein) NR: not reported BMI: body mass index NSAIDs: non-steroidal anti-inflammatory drugs C/S: corticosteroids DMARDs: disease-modifying anti-rheumatic drugs SD: standard deviation		

6.3.2 Baseline statistics

Table 6.4 (p.174) demonstrates all outcome measures used in this study at baseline (Test 1). Because there were significant differences of HAQ-DI and HADs between groups at baseline, change scores were calculated for all outcome

measures between Tests 1 and 2; Tests 1 and 3; Tests 2 and 3, and were subsequently used for data analysis.

Table 6.4: Mean (SD)/median (IQR) comparison of outcome measures between groups at baseline (Test 1).

Variables	Hydrotherapy (n = 21)	Land (n = 22)	p (95% CI)
Primary outcome measure			
Functional ability			
HAQ-DI [†]	1.9 (0.6)	1.4 (0.7)	0.023 (-0.9 to -0.1)
Secondary outcome measures			
HAQ _{VAS} [†] (Pain)	55 (24)	45 (28)	0.208 (-26 to 5.9)
HAQ-GWB [†] (Wellbeing)	57 (22)	42 (26)	0.056 (-29 to 0.37)
Quality of life:			
EQ-5D tariff [*]	0.587 (0.43)	0.587 (0.59)	0.434
EQ-5D _{VAS} [†]	52 (18)	52 (30)	0.940 (-16 to 15)
Disease activity:			
DAS28 [†]	4.28 (1.8)	4.31 (1.6)	0.960 (-1.1 to 1.1)
RADAI [†]	4.5 (2.3)	3.9 (2.4)	0.355 (-2.1 to 0.77)
Mood symptoms:			
HAD scale [*]	13 (10.5)	9 (12)	0.037
HAD-D [*]	7 (5)	4 (5.5)	0.122
HAD-A [*]	7 (6.5)	5 (6.25)	0.078
[†] Values are in mean (SD) and by independent t-test [*] values are in median (IQR) and by Mann-Whitney u-test Significant p values are indicated in boldface Key: HAQ-DI overall scores (0-3), with 0 being best, and 3 worst functioning HAQ _{VAS} score (0-100), 0 being no pain, and 100 being severe pain HAQ GWB scores (0-100), 0 being very well, and 100 being very poor EQ-5D tariff score (-0.594-1), with 1 being perfect health, and -0.594 being worse than death EQ-5D _{VAS} score (0-100), with 0 being low quality, and 100 being high quality RADAI overall score (0-10), with 0 being no disease activity, and 10 being very severe DAS28 overall score (0 -9.4), with 0 being no disease activity, and 9.4 being very severe HAD overall score (0-42), with 0 being no depression and/or anxiety, and 42 being very severe depression and/or anxiety HAD-D overall score (0-21), with 0-7 being normal, 8-10 being a borderline case, and ≥ 11 a definite case HAD-A overall score (0-21), with 0-7 being normal, 8-10 being a borderline case, and ≥ 11 definite a definite case			

From the eight categories of HAQ-DI at baseline (Test 1), only three categories showed significant differences between the two groups: eating ($p = 0.011$), walking ($p = 0.012$) and hygiene ($p = 0.034$) (Table 6.5).

Table 6.5: HAQ-DI categories between hydrotherapy and land-therapy group at Test 1.

HAQ-DI categories	Hydrotherapy (n = 21) Mean (SD)	Land therapy (n = 22) Mean (SD)	p (95% CI)
Dressing & Grooming	1.6 (0.8)	1.3 (0.9)	0.239 (-0.80 to 21)
Arising	1.5 (0.7)	1 (0.8)	0.062 (-0.88 to 0.02)
Eating	1 (0.7)	1 (0.8)	0.011 (-1 to -0.14)
Walking	1.9 (0.6)	1.2 (1)	0.012 (-0.3 to -0.17)
Hygiene	2 (0.6)	1.4 (1)	0.034 (-1.1 to -0.05)
Reach	1.9 (0.8)	1.6 (1)	0.259 (-0.87 to 0.24)
Grip	1.8 (0.6)	1.5 (0.9)	0.178 (-0.77 to 0.15)
Activities	2 (0.9)	1.6 (1)	0.109 (-1 to 0.11)
Key: HAQ-DI overall scores (0 to 3), with 0 being best and 3 worst functioning Significant p values are indicated in boldface			

6.3.3 Post-treatment and follow-up statistics

6.3.3.1 Primary outcome measure (HAQ-DI) - between groups

For the primary outcome measure, comparisons were made using the mean (SD) change score of HAQ-DI (between Tests 1 and 2) in both groups. Table 6.6 (p.176) displays the change score of HAQ-DI between the two groups. There were significant differences in the HAQ-DI change score in the hydrotherapy group compared to the land-therapy group ($p < 0.001$), indicating that patients experienced a greater benefit from the hydrotherapy than those patients who received the land therapy.

Table 6.6: Comparison of HAQ-DI change score between groups (Tests 1 & 2).

Variables	Hydrotherapy (n = 21)			Land (n = 22)			P (95% CI)
Primary outcome	T1	T2	Change score	T1	T2	Change score	
HAQ-DI [†]	1.9 (0.6)	1.1 (0.7)	0.7 (0.8)	1.4 (0.7)	1.4 (0.8)	-0.02 (0.4)	< 0.001 (-1.1 to -0.4)
[†] Values are in mean (SD) and by independent t-test for change score Significant p values are indicated in boldface Key: HAQ-DI overall scores (0-3), with 0 being best, and 3 being worst functioning T1: Test 1 at baseline T2: Test 2 post-treatment							

The change score of HAQ-DI between Tests 1 and 3, and Tests 2 and 3, revealed no significant differences in both groups (Appendix 23 and 24, respectively). This means that there was no improvement of HAQ-DI in the follow-up period of three months, either in post-hydrotherapy or land therapy.

Moreover comparing the change score for each category of HAQ-DI between Tests 1 and 2 showed that there were significant differences in five categories of HAQ-DI, namely dressing and grooming, walking, hygiene, reach and activities. This indicated that most functional ability dimensions of HAQ-DI revealed a decline in this score, and hence an improvement in patients' functional ability after hydrotherapy (Table 6.7, p.177).

Table 6.7: Comparison of HAQ-DI categories in change score between groups (Tests 1 & 2).

HAQ-DI categories	Hydrotherapy group (n= 21)			Land group (n = 22)			p (95% CI)
	Mean (SD)			Mean (SD)			
	T1	T2	Change score*	T1	T2	Change score*	
Dressing & grooming	1.6 (0.8)	1.1 (0.8)	0.5 (0.81)	1.3 (0.9)	1.3 (0.9)	-0.05 (0.72)	0.032 (-0.99 to -0.05)
Arising	1.5 (0.7)	1 (0.7)	0.5 (0.7)	1 (0.8)	1(0.8)	0.09 (0.68)	0.071 (-0.31 to 0.76)
Eating	1 (0.7)	1 (0.6)	-0.24 (0.8)	1 (0.8)	1.3 (0.8)	-0.09 (1.3)	0.650 (-0.50 to 0.80)
Walking	1.9 (0.6)	0.9 (0.6)	1 (0.6)	1.2 (1)	1.3 (1)	-0.14 (0.9)	< 0.001 (-1.7 to -0.54)
Hygiene	2 (0.6)	1.3(1.1)	0.7 (0.90)	1.4 (1)	1.5 (1)	-0.1 (0.7)	0.001 (-1.3 to -0.35)
Reach	1.9 (0.8)	1.2 (0.9)	0.7 (1.2)	1.6 (1)	1.7 (1)	-0.09 (0.75)	0.019 (-1.4 to -0.13)
Grip	1.8 (0.6)	1.4 (0.7)	0.4 (0.9)	1.5 (0.9)	1.4 (0.9)	0.09 (0.75)	0.180 (-0.84 to 0.16)
Activities	2.1 (0.9)	1.3 (1)	0.8 (0.9)	1.6 (1)	1.6 (1)	0 (0.62)	0.004 (-1.3 to -0.26)
*Independent t-test of change score difference							
Significant p values are indicated in boldface							
Key:							
T1: Test 1 at baseline							
T2: Test 2 post-treatment							

6.3.3.2 Primary outcome measure (HAQ-DI) - within groups

No significant differences in HAQ-DI scores were shown within the land-therapy group for the HAQ-DI (Appendix 21). Within the hydrotherapy group, significant differences in HAQ-DI scores were found between Tests 1 and 2 only ($p = 0.014$), meaning that the functional ability of RA patients was improved immediately after hydrotherapy (Table 6.8). However, this improvement was not statistically significant under Tests 1 and 3 or Tests 2 and 3.

Table 6.8: Results of one-way repeated measures ANOVA of HAQ-DI in the hydrotherapy group between Tests 1, 2 & 3.

HAQ-DI			
Statistics	Test 1	Test 2	Test 3
Mean	1.9	1.1	1.3
SD	0.6	0.7	0.6
F	5.998		
df	2		
p-value	0.003		
p* (95% CI)	Test 1 - Test 2 0.014 (0.127 to 1.170)	Test 1 - Test 3 0.088 (-0.064 to 1.114)	Test 2 - Test 3 0.989 (-0.457 to 0.211)
<p>*p-value based on adjustment for Bonferroni set at 0.017 (0.05/3) Significant p values are indicated in boldface</p> <p>Key:</p> <p>HAQ-DI overall scores (0-3), with 0 being best functioning, and 3 being worst functioning SD: Standard deviation F: F-statistics DF: Degree of freedom Test 1 (baseline) Test 2 (post-treatment) Test 3 (three-months follow up)</p>			

6.3.3.3 Secondary outcome measures - between groups

HAQ_{VAS} (pain)

Change score of pain was significant between Tests 1 and 2 ($p < 0.001$) in the hydrotherapy group compared to the land-therapy group (Table 6.9, p.180). This indicates that patients experienced greater benefits and relief of pain in the hydrotherapy compared to those in the land-therapy group.

HAQ-GWB (wellbeing)

Change scores were significantly different in the hydrotherapy group compared to the land-therapy group ($p < 0.001$) (Table 6.9, p.180). This means that RA patients had better improvements from the hydrotherapy treatment than from the land therapy treatment.

EQ-5D_{VAS} (QoL)

The mean change score between Test 1 and 2, showed significant improvement ($p = 0.021$) (Table 6.9, p.180). Patients in the hydrotherapy group experienced a significantly greater improvement in general health status compared to those in the land-therapy group.

EQ-5D tariff (QoL)

Patients in both groups did not experience any change in HRQoL between Test 1 and 2 measured by the EQ-5D tariff (Table 6.9, p.180).

Table 6.9: Comparison of secondary outcome measures in change score between groups (Tests 1 & 2).

Variables	Hydrotherapy group (n= 21) †Mean (SD) *Median (IQR)			Land group (n = 22) †Mean (SD) *Median (IQR)			p (95% CI)
	T1	T2	Change score	T1	T2	Change score	
HAQ _{VAS} [†] (pain) HAQ-GWB [†] (wellbeing)	55 (24) 57 (22)	35.5 (18.3) 33 (18)	20 (21) 24 (21)	45 (28) 42 (26)	54 (28) 51 (27)	-9 (20) -9 (23)	< 0.001 (-41 to -16) < 0.001 (-46 to -19)
Health status (QoL)							
EQ-5D tariff *	0.587 (0.43)	0.587 (0.17)	0 (0.21)	0.587	0.587 (0.58)	0 (0.52)	0.842
EQ-5D _{VAS} [†]	52 (18)	73 (11)	-14 (13)	52 (30)	54 (24)	2 (33)	0.021 (3 to 34)
Disease activity							
DAS28 [†]	4.28 (1.78)	2.49 (1.24)	1.8 (1.7)	4.31 (1.57)	3.28 (1.38)	1 (2.3)	0.613 (-1.6 to 0.94)
RADAI [†]	4.5 (2.3)	4 (2.7)	0.5 (2.75)	3.9 (2.4)	4.5 (2.2)	-0.6 (1.56)	0.094 (-2.5 to 0.20)
Mood symptoms							
HAD scale*	13 (10.5)	12 (7.5)	1 (8)	9 (12)	12 (7)	-3 (9.5)	0.023
HAD-D*	7 (5)	6 (5)	1 (3)	4 (5.5)	7 (3)	-2 (4.25)	0.042
HAD-A*	7 (6.5)	7 (5)	0 (6)	5 (6.25)	7 (3.5)	-2 (4.25)	0.038
<p>†Values are in mean (SD) and by independent t-test for change score *values are in median (IQR) and by Mann-Whitney u-test for change score Significant p values are indicated in boldface</p> <p>Key:</p> <p>HAQ_{VAS} score (0-100), 0 being no pain, 100 being severe pain HAQ GWB scores (0-100), 0 being very well, 100 being very poor EQ-5D tariff score (0.594-1), with 1 being perfect health, 0.594 being worse than death EQ-5D_{VAS} score (0-100), with 0 being low quality, and 100 being high quality RADAI overall score (0-10), with 0 being no disease activity, and 10 being very severe disease activity DAS28 overall score (0-9.4), with 0 being no disease activity, and 9.4 very severe disease activity HAD overall score (0-42), with 0 being no depression and/or anxiety, 42 being very severe depression, and/or anxiety) HAD-D overall score (0-21), with 0-7 being normal, 8-10 being a borderline case, ≥ being a 11 definite case HAD-A overall score (0-21), with 0-7 being normal, 8-10 being a borderline case, ≥ being a 11 definite case</p>							

EQ-5D Dimensions (QoL)

The descriptive part of EQ-5D dimension was compared between hydrotherapy and land therapy at Test 1, Test 2 and Test 3. Because the numbers of reported level-three 'extreme problems' were very low among participants, the EQ-5D levels were dichotomised into 'no problems' and 'problems' rather than 'no problems', 'moderate problems' or 'extreme problems' (EuroQol Group, 1990; Rabin et al., 2011a). Each subject per dimension could choose only one category (no problems, moderate problems or extreme problems).

The graphs below show participants who reported no problems or problems in the five EQ-5D dimensions. At Test 1, results show that the high percentage of patients who experienced 'problems' revealed in the dimension of mobility, usual activity and pain in both groups (Figure 6.2, p.182 and Figure 6.3, p.182). The percentage of patients who reported problems in anxiety and depression increased in the hydrotherapy group compared with the land-therapy group (Figure 6.2, p.182 and Figure 6.3, p.182). At Test 2, few differences appeared between the two groups except in the pain dimension. Here, the percentage of patients who reported problems in pain and discomfort decreased markedly from 81% to 66.7%, which means that there is some favourable improvement to pain level in the hydrotherapy group (Figure 6.2, p.182). Moreover, in spite of the small sample size of the three-month follow-up period (14 in the hydrotherapy group and 14 in the land-therapy group), the percentage of respondents who reported problems in pain level decreased clearly in the hydrotherapy group from 66.7% to 28.6% (Figure 6.2, p.182). No obvious marked change was noticed in other dimensions in either group. Thus, only the pain dimension in the hydrotherapy

group showed improvement over time compared to the land-therapy group. However, the other dimensions fluctuated over time in both groups.

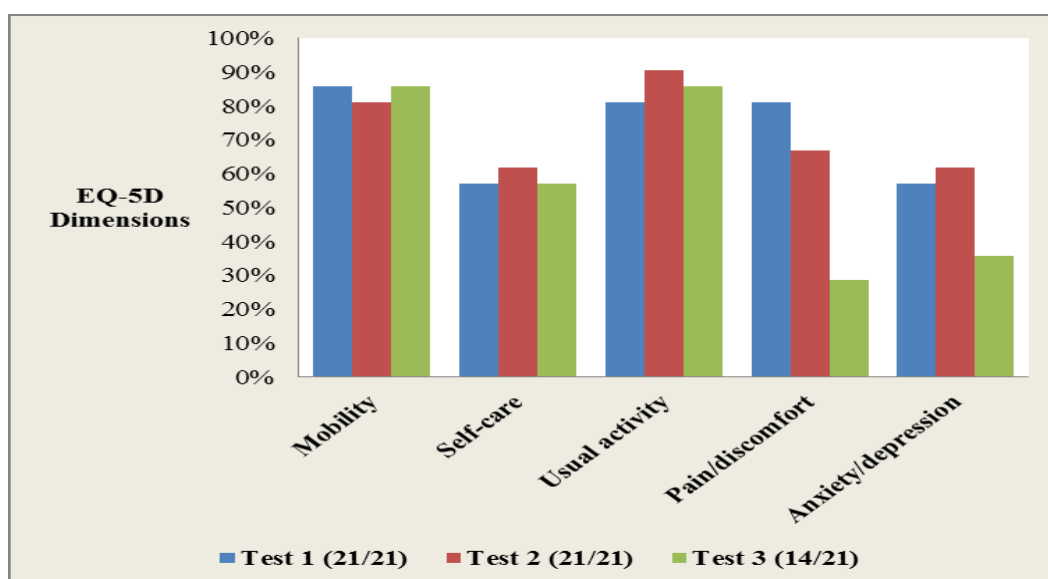


Figure 6.2: Percentage of patients recording 'problems' to EQ-5D questions in the hydrotherapy group.

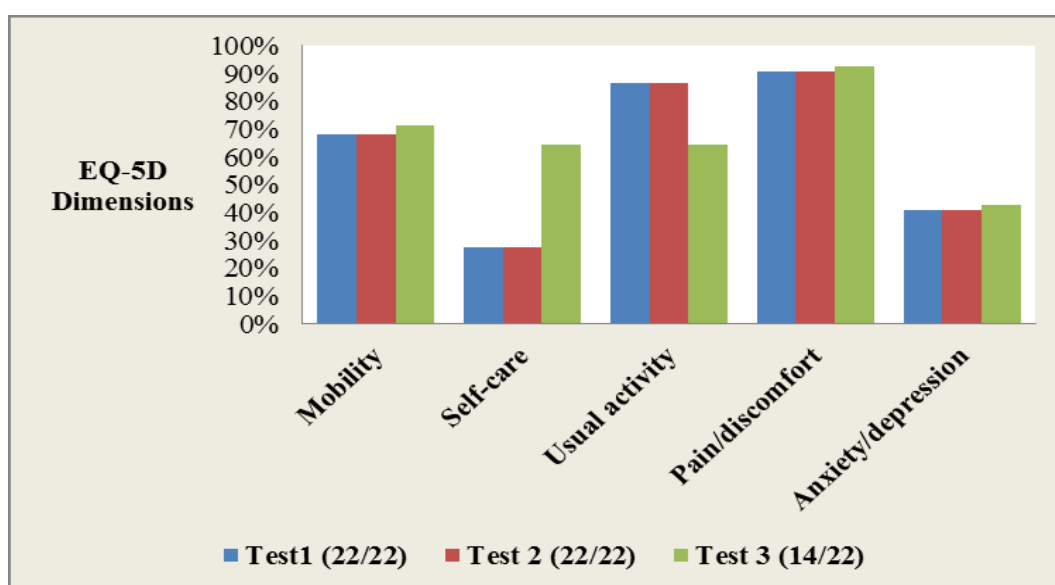


Figure 6.3: Percentage of patients recording 'problems' to EQ-5D questions in the land-therapy group.

DAS28 (disease activity)

The overall score of DAS28 declined from 4.28 in Test 1 to 2.49 in the hydrotherapy group, compared to 4.31 in Test 1 to 3.28 in Test 2 for the land-therapy group (Table 6.9, p.180). The change score was not significant ($p = 0.613$). However, in spite of no significant finding, this may be clinically important due to the fact that a DAS28 score of less than 2.6 corresponds to the remission stage of disease activity, and patients who begun the hydrotherapy treatment with a mean DAS28 score of 4.28 actually experienced a trend of remission in disease activity post-treatment. This trend, however, was not seen in post-treatment land therapy patients.

RADAI (disease activity)

RADAI did not detect any significant difference in change score between the hydrotherapy group and land-therapy group ($p = 0.094$), which indicates that disease activity measured by the self-administered questionnaire was not affected by hydrotherapy treatment compared to land therapy treatment (Table 6.9, p.180).

Mood symptoms (HADs, HAD-D, HAD-A)

Change scores of anxiety and depression between Test 1 and Test 2 showed significant differences (Table 6.9, p.180), indicating that changes in mood were significantly better in the hydrotherapy group compared to those in the land-therapy group.

6.3.3.4 Secondary outcome measures – within groups

Three of the secondary outcome measures, HAQ_{VAS}, HAQ-GWB and EQ-5D_{VAS}, showed significant differences within the hydrotherapy group (Appendix 21).

No significant differences in the secondary outcome measures were shown within the land-therapy groups (Appendix 21).

HAQ_{VAS} within group

Within the hydrotherapy group, significant changes were found for HAQ_{VAS} between Tests 1 and 2 only ($p = 0.015$) (Table 6.10). However, at Test 3 the VAS score was reduced to 40 ± 26.5 which was not statistically significant different from Test 1 ($p = 0.137$) nor Test 2 ($p = 0.556$). These findings suggest that after six weeks of intervention, a significant reduction in pain score was observed, but this was not sustained at three months.

Table 6.10: Results of repeated measures ANOVA of HAQ_{VAS} in the hydrotherapy group between Tests 1, 2 & 3.

HAQ_{VAS}			
Statistics	Test 1	Test 2	Test 3
Mean	55	35.5	40
SD	24	18.3	26.5
F	4.882		
df	2		
p-value	0.004		
p* (95% CI)	Test 1 - Test 2 0.015 (3.9 to 39.1)	Test 1 - Test 3 0.137 (-3.7 to 34)	Test 2 - Test 3 0.556 (-18.5 to 6)
<p>*p-value based on adjustment for Bonferroni set at 0.017 (0.05/3) Significant p values are indicated in boldface</p> <p>Key:</p> <p>HAQ_{VAS} score (0-100), 0 being no pain, 100 being severe pain SD: Standard deviation F: F-Statistics DF: Degree of freedom Test 1 (baseline) Test 2 (post-treatment) Test 3 (three-months follow up)</p>			

HAQ-GWB

In the hydrotherapy group, it can be seen that the HAQ-GWB was confirmed to be significant as shown by the repeated measure ANOVA, where p-value = 0.002 (Appendix 21). From the post-hoc test, the significant differences were observed between Tests 1 and 2 ($p = 0.002$) and at Tests 2 and 3 ($p = 0.027$) (Table 6.11, p.186). However, at Test 3 the GWB score was reduced to 44.2 ± 19.3 which was statistically significantly different from Test 2 ($p = 0.027$), but not significant at Test 1 ($p = 0.126$). This indicated that the improvement in GWB is observed to be significant over time.

Table 6.11: Results of repeated measures ANOVA of HAQ-GWB in the hydrotherapy group between Tests 1, 2 & 3.

HAQ-GWB			
Statistics	Test 1	Test 2	Test 3
Mean	57	33	44.2
SD	22	18	19.3
F	5.084		
df	2		
p-value	0.002		
p* (95% CI)	Test 1 - Test 2 0.002 (9.8 to 41)	Test 1 - Test 3 0.126 (-3.3 to 33.6)	Test 2 - Test 3 0.027 (-19 to -1.1)
<p>*p-value based on adjustment for Bonferroni set at 0.017 (0.05/3) Significant p values are indicated in boldface</p> <p>Key:</p> <p>HAQ GWB scores (0 – 100), 0 being very well, and 100 being very poor SD: Standard deviation F: F-Statistics DF: Degree of freedom Test 1 (baseline) Test 2 (post-treatment) Test 3 (three months follow-up)</p>			

EQ-5D_{VAS}

In the hydrotherapy group, the EQ-5D_{VAS} was confirmed to be significant as shown by the repeated measure ANOVA, where p-value = 0.009 (Appendix 21). Additionally, from the post-hoc analysis, the significant differences was found between Test 1 and Test 2 (p = < 0.001). This finding indicated that there was an improvement in HRQoL between baseline and post intervention (73 ± 11 vs. 52 ± 18) (Table 6.12).

Table 6.12: Results of repeated measures ANOVA of EQ-5D_{VAS} in the hydrotherapy group between Tests 1, 2 & 3.

EQ - 5D _{VAS}			
Statistics	Test 1	Test 2	Test 3
Mean	52	73	66.4
SD	18	11	18.4
F	4.251		
df	2		
p-value	0.009		
p* (95% CI)	Test 1 - Test 2 < 0.001 (-29.3 to -13.7)	Test 1 - Test 3 0.179 (-33 to 4.7)	Test 2 - Test 3 0.699 (-8.8 to 23.5)
*p-value based on adjustment for Bonferroni set at 0.017 (0.05/3) Significant p values are indicated in boldface Key: EQ-5D _{VAS} score (0-100), 0 being low quality, and 100 being high quality SD: Standard deviation F: F-Statistics DF: Degree of Freedom Test 1 (baseline) Test 2 (post treatment) Test 3 (3 months follow up)			

In summary, patients with RA in the hydrotherapy group were found to have experienced significantly greater improvements in functional ability, pain, GWB, health status and psychological wellbeing, compared to the land-therapy group immediately post treatment.

6.3.4 Correlation Results

6.3.4.1 Relationship between RADAI and DAS28 at Test 2

When looking at disease activity and observing patients conditions in both groups, there emerged a statistically significant positive relationship of disease activity between the DAS28 and RADAI ($r = 0.328$, $p = 0.032$). However, when looking at this correlation in both groups separately, a moderate and statistically significant correlation was found between DAS28 and RADAI in the land-therapy group at Test 2 ($r = 0.501$, $p = 0.018$), however, no correlation was observed in the hydrotherapy group ($r = 0.145$, $p = 0.529$) (Table 6.13). These findings indicate that while the scores from those self-administered questionnaires that measure disease activity (such as RADAI) may reflect or correlate with other tools used by physicians or health professionals when assessing disease activity, they may, however, not necessarily be compatible with the same score measuring the same index.

Table 6.13: *Pearson's correlations between (RADAI & DAS28) at Test 2.

RADAI			
	Hydrotherapy group (n = 21)	Land-therapy (n = 22)	All patients n = 43
DAS28	$r = 0.145$ $p = 0.529$	$r = 0.501$ $p = 0.018$	$r = 0.328$ $p = 0.032$
Key: r = Pearson's correlation coefficient [$\pm r < 0.30$ = low; $\pm 0.30 < r < 0.60$ = moderate) and $\pm r > 0.60$ = high] Significant p values are indicated in boldface *Pearson's correlation was carried out because both DAS28 & RADAI are normally distributed at Test 2 RADAI overall score (0 – 10), with 0 no disease activity and 10 very severe DAS28 overall score (0 -9.4), with 0 no disease activity and 9.4 very severe			

6.3.4.2 Relationship between depression score (HAD-D) and: educational levels, disease duration, morning stiffness, RF and disease activity indexes in patients with RA

In Study One, the prevalence of depression at baseline was found to be 35% ($n = 15/43$), which is relatively higher compared with that reported in the literature (Covic et al., 2012; Mella et al., 2010) (Table 6.3, p.173). The researcher hypothesised that there was a relationship between the depression score and low EL, severe MS, longer DD, positive RF, a high DAS28 score and a high RDAI score.

To investigate the degree of relationship between the score of depression in Test 2 with these variables, Spearman's correlation coefficient was carried out (as the depression score (HAD-D) was not normally distributed in Test 2 (Appendix 20). There was not any statistically significant correlation of the depression score with all variables, with the exception that there was a moderate positive correlation between depression (HAD-D) and RDAI in the land-therapy group ($r = 0.502$, $p = 0.017$), and using all data ($r = 0.578$, $p < 0.001$) respectively. In the hydrotherapy group, moderate positive correlation was found between HAD-D and RDAI ($r = 0.465$, $p = 0.033$) (Table 6.14, p.189).

Table 6.14: *Spearman's correlations between depression score (HAD-D) in Test 2 with other demographic data and outcome variables.

Variables	Hydrotherapy group (n = 21)		Land-therapy group (n = 22)		All patients (n = 43)	
	p	r	p	r	p	r
HAD-D & ELs	0.425	-0.340	0.121	-0.184	0.075	-0.275
HAD-D & MS	0.118	-0.352	0.873	0.036	0.245	-0.118
HAD-D & DD	0.645	-0.162	0.472	-0.107	0.385	-0.136
HAD-D & RF	0.666	-0.100	0.485	0.157	0.782	0.043
HAD-D & DAS28	0.784	0.064	0.359	0.205	0.289	0.166
HAD-D & RADAI	0.033	0.465	0.017	0.502	< 0.001	0.578
<p>*Spearman's correlation coefficient [$\pm r < 0.30$ = low; $\pm 0.30 < r < 0.60$ = moderate) and $\pm r > 0.60$ = high]. Significant p values are indicated in boldface</p> <p>Key:</p> <p>HAD-D: Depression ELs: Educational levels MS: Morning stiffness RF: Rheumatoid factor DD: Disease duration DAS28: Disease Activity Score 28 RADAI: Rheumatoid Arthritis Disease Activity Index</p>						

6.3.4.3 Relationship between anxiety score (HAD-A) and: educational levels, disease duration, morning stiffness, RF and disease activity indexes in patients with RA

In Study One, the prevalence of anxiety was found to be 30% ($n = 13/43$), which is relatively similar compared with those found in the literature (Covic et al., 2012; Mella et al., 2010). Spearman's Correlation coefficient was carried out as anxiety score (HAD-A) post-treatment was not normally distributed (Appendix 20) to find out any association between anxiety score post-treatment with variables in categorical data and outcome measures in the previous section.

Table 6.15 (p.191) showed no association between anxiety score and EL, MS, DD, RF and DAS28. The only exception was that there was a moderate positive association between anxiety score (HAD-A) and disease activity measured by RADAI in the land-therapy group ($r = 0.544$, $p = 0.009$), a moderate positive association with all patients ($r = 0.425$, $p = 0.005$).

This significant positive correlation indicates that patients who have high scores of anxiety may also present with high scores of disease activity in the land-therapy group. However, these results were not very convincing, as this finding was not discovered in patients in the hydrotherapy group ($r = 0.320$, $p = 0.157$).

Table 6.15: *Spearman's correlations between anxiety score (HAD-A) in Test 2 with other demographic data and outcome variables.

Variables	Hydrotherapy group (n = 21)		Land-therapy group (n = 22)		All patients (n = 43)	
	p	r	p	r	p	r
HAD-A & ELs	0.362	-0.210	0.295	- 0.234	0.169	-0.214
HAD-A & MS	0.922	0.023	0.874	0.036	0.912	0.017
HAD-A & DD	0.523	-0.148	0.184	-0.294	0.227	-0.188
HAD-A & RF	0.802	-0.058	0.813	0.054	0.994	-0.001
HAD-A & DAS28	0.302	-0.237	0.879	0.034	0.580	-0.087
HAD-A & RADAI	0.157	0.320	0.009	0.544	0.005	0.425
*Spearman's correlation coefficient [$\pm r < 0.30$ = low; $\pm 0.30 < r < 0.60$ = moderate) and $\pm r > 0.60$ = high] Significant p values are indicated in boldface Key: HAD-A: Anxiety ELs: Educational levels MS: Morning stiffness RF: Rheumatoid factor DAS28: Disease Activity Score 28 RADAI: Rheumatoid Arthritis Disease Activity Index						

In summary, no significant correlation was found between the depression or anxiety score in Test 2 except for disease activity measured by RADAI. This should be interpreted with care, as other parameters of disease activity showed no correlation.

6.3.5 Results of regression analyses

Table 6.16 (p.192) shows results of multivariate regression analysis of detailed independent variables when combined in the model. The GWB was the only predictor of functional disability in patients with RA $p < 0.003$. Multiple

regression analysis results in a lower chance of predicting relationship because of the overlapping of symptoms and interaction of variables (Field, 2009).

Table 6.16: Predictors of functional abilities of the (HAQ-DI) in patients with RA (multiple-regression analysis).

Variables	Beta	SE	P (95% CI)
Depression score	0.157	0.034	0.410 (-0.041 to 0.099)
Anxiety score	0.308	0.029	0.068 (-0.004 to 0.112)
RADAI	-0.054	0.064	0.799 (-0.146 to 0.113)
HAQ-GWB	0.467	0.004	0.003 (0.005 to 0.002)
EQ-5D tariff	-0.044	0.304	0.766 (-0.706 to 0.524)
<p>Multiple regression analysis refers to predictive relationship (Beta). Significant p values are indicated in boldface. SE refers to standard error</p> <p>Key:</p> <p>HAQ-DI overall scores (0 to 3), 0 being best functioning, and 3 being worst functioning HAQ GWB scores (0–100), 0 being very well, 100 being very poor EQ-5D tariff score (0.594 to 1), 1 being perfect health, -0.594 being worse than death RADAI overall score (0–10), 0 being no disease activity, and 10 being very severe disease activity HAD-D overall score (0-21), 0-7 being normal, 8-10 being a borderline case, ≥ 11 being a definite case HAD-A overall score (0-21), 0-7 being normal, 8-10 being a borderline case, ≥ 11 being a definite case</p>			

Table 6.17 (p.193) shows results of univariate regression analysis detailing variables with significant predictive effects on functional abilities. Higher depression and anxiety scores, RADAI, HAQ-GWB, and low EQ-5D tariff scores were associated with increased functional disability in patients with RA all with $p < 0.001$. However, the following variables that were tested using both multiple and univariate regression analyses were identified as not being predictors of functional disability such as age, gender, ELs, smoking, HT, BMI, DD, medication, marital status, DAS28, EQ-5D_{VAS} or HAQ_{VAS}.

Table 6.17: Predictors of functional abilities of the (HAQ-DI) in patients with RA (univariate regression analysis).

Variables	Beta	SE	P (95% CI)
Depression score	0.544	0.024	< 0.001 (0.051 to 0.148)
Anxiety score	0.513	0.023	< 0.001 (0.042 to 0.137)
RADAI	0.561	0.039	< 0.001 (0.091 to 0.250)
HAQ-GWB	0.603	0.004	< 0.001 (0.010 to 0.025)
EQ-5D tariff	-0.396	0.300	0.009 (-1.433 to -0.233)
Univariate beta analysis refers to predictive relationship indicated in boldface (second column) Significant p values are indicated in boldface (fourth column) SE refers to standard error Key: HAQ-DI overall scores (0 to 3), 0 being best functioning, and 3 being worst functioning HAQ GWB scores (0–100), 0 being very well, 100 being very poor EQ-5D tariff score (0.594 to 1), 1 being perfect health, -0.594 being worse than death RADAI overall score (0–10), 0 being no disease activity, and 10 being very severe HAD-D overall score (0–21), 0–7 being normal, 8–10 being a borderline case, ≥ 11 being a definite case HAD-A overall score (0–21), 0–7 being normal, 8–10 being a borderline case, ≥ 11 being a definite case			

6.3.6 Exercise programmes

Appendix 25 describes the intervention programme in the hydrotherapy and land-therapy group. It illustrates the exercises tailored and designed for participants according to patients' condition and capability. It is essential to emphasise that warm-up and cool-down exercises are not included here, as these were performed by all the participants. In both groups, it can be seen that exercise treatment details, aims and goals were similar. The only exception was that 14 out of 21 in hydrotherapy group were provided with education on how to manage flare-ups compared to eight out of 22 in the land-therapy group.

6.4 Overall summary of results

This chapter has discussed the results of physical function (functional ability, pain, GWB), disease activity (self-administered and physician disease activity tool), mood changes (psychological wellbeing) and QoL (health status) in patients with RA. Patients with RA in the hydrotherapy group were found to have experienced significant improvements in functional ability, pain, GWB, health status and psychological wellbeing (i.e. lower HAQ-DI, lower HAQ-GWB, lower HAQ_{VAS}, high EQ-5D_{VAS} and lower HADs) compared with the land-therapy group. However, no differences were revealed in change score in disease activity measured by DAS28 and RADAI, HRQoL measured by the EQ-5D tariff. These findings indicate that patients with RA in the hydrotherapy group exhibited improvement in physical function, HRQoL and psychological wellbeing. HAQ-DI change score categories showed improvement in five categories between Tests 1 and 2.

While a moderate relationship was found between disease activity parameters (DAS28 and RADAI) in all patients in the land-therapy group, no relationship was found in the hydrotherapy group. Caution must be exercised in the interpretation of the current findings because of the contradictory result revealed and the small sample size. As expected, the moderate correlation between depression score and disease activity parameter (RADAI) clearly appeared in the land-therapy group and in all patients in Test 2. Moreover, a moderate correlation was found between anxiety score and RADAI in the land-therapy group and all patients at Test 2. Conversely, the anxiety score post-treatment failed to find this correlation in the hydrotherapy group only. A number of variables that were

identified to be predictive of functional disability were RADAI, depression, anxiety, GWB and EQ-5D tariff. Exercise intervention in both groups was undertaken with the patients stating both what they were aiming or planning to achieve in order to increase compliancy by attempting to have the motivation to continue to perform the HEP.

The next chapter describes epidemiological characteristics of patients referred to hydrotherapy and the Kellgren Centre patients (Study Two).

CHAPTER SEVEN: WHAT TYPES OF RHEUMATOID ARTHRITIS (RA) PATIENTS ARE REFERRED FOR HYDROTHERAPY? (STUDY TWO)

7.1 Introduction

The Kellgren Centre of Rheumatology is the main rheumatology department within central Manchester. It is responsible for diagnoses, treatment, referrals, and consultation for all rheumatic and musculoskeletal diseases such as connective tissue disease, psoriatic arthropathies, ankylosing disease, inflammatory arthritis disease, hypermobility syndrome, RA disease and crystal-induced arthropathies. The Kellgren Centre of Rheumatology at Manchester Royal Infirmary (MRI) within the CMFT is named after Professor Kellgren, the first Professor of Rheumatology in the UK. Professor Kellgren, a former Dean of the medical school helped to establish the first University Department of Rheumatology in the country at the CMFT in the late 1940s.

When studying RA epidemiological profiles (descriptive epidemiology), there are many potential risk factors for RA, depending on the occurrence and variation of the disease. These include age, gender, social support group (occupational status, marital status) as well as duration of disease onset, influence of genetic or environmental risk factors such as smoking, RF, DAS28, and HT.

Although a power calculation was performed for Study One (Chapter 5, p.163), the intended sample size was not reached. It was felt to be important that a comparison to a large sample of RA patients was necessary to support the external

validity of the findings from Study One. This second study, therefore describes the characteristics of those patients referred to hydrotherapy in Study One from Salford Royal NHS Foundation Trust (SRFT) and compares them to patients from the Kellgren Centre and previous rheumatology studies in order to find out whether the features of Study One participants reflect those of a large regional centre in England and other international studies.

Aims of Study Two

The aim of this study is to:

- Describe and compare the characteristics of patients from Study One to a representative cohort of patients from a regional rheumatology centre and previous rheumatology studies.

7.2 Method

7.2.1 Population

In order to carry out this study, collecting information from a sample of 10%, $n = 200$, of all patients at the Kellgren Centre was proposed. A sample of 200 was chosen because, firstly, it was a manageable number of records to collect in the time available, and secondly, this number gives a margin of error of 0.071 or 7.1%, which was deemed acceptable (Niles, 2006). This means that if our random sample has an average age of 70 years, there is 95% probability that the average age of all patients is between 62.9 and 77.1 years.

All the information was selected from the medical notes randomly and anonymised. The research nurse at the Kellgren Centre selected the notes from those patients attending clinics over a three-month period and completed a data

form (Appendix 26). No medical notes were removed from the Kellgren Centre and access to them was limited to the relevant authorised consultants and nurses. To preserve confidentiality and anonymity, the researcher did not know whose information was selected because no names and no identifiable patient information were used.

This study had ethical approval from the North West 2 Research Ethics Committee-Liverpool Central (Appendix 29) with agreement of clinicians in the Kellgren Centre (Appendix 28). A letter was sent out to all patients to inform them that their notes might be selected and used for research purposes, and they were given the choice of opting out (Appendix 27).

The information obtained from the medical notes included:

- Age
- Gender
- DD
- Occupational status (e.g. retired/working)
- Current treatment (medication)
- Body mass index (BMI) (height and weight)
- DAS28 (if recorded)
- RF (if recorded)
- HT
- Smoker or non-smoker
- Marital status

The above data were transferred to the University and stored on password-protected computers stored in lockable rooms. The information was grouped together and only the averages and frequencies of all the data gathered were reported, so individual characteristics were not described. The researcher looked at some parts of the data collected for the study; authorised people (clinicians, nurses and research development staff) were also able to look at the data from CMFT to check that the study was being carried out correctly. Demographic data are essential in each study as part of the comparison between the general RA population and those referred to hydrotherapy, these data are commonly collected in research studies in RA patients and have relevance for clinicians with regard to their practice (Silman & Pearson, 2002).

7.2.2 Rationale for outcomes

RA is a chronic disease that influences all the aspects of the lives of patients, whether physically, psychologically or socially (Fitzpatrick et al., 1991; NICE, 2009). There has been substantial recent interest in understanding the epidemiology of RA. There have been several population studies in different countries around the world (Figure 2.1, p.37 and Table 2.3, p.38), and facets of differential occurrence have stimulated a number of analytical studies looking for both genetic and environmental risk factors for RA patients (Silman & Pearson, 2002). The outcomes in Study Two were chosen because: 1) they are commonly reported in the medical notes, 2) they have been reported on in previous studies, and 3) they might affect a patient's disease process or rehabilitation.

Marital status: It has been suggested in many studies that social support is significant to the patients' psychosocial adjustment and mental health (Affleck et

al., 1988; Fyrand et al., 1997; Goodenow et al., 1990). These studies recommended the need for more research about the potential negative impact of a lack of social support on the treatment of this chronic disease. The importance of marital status in predicting and explaining health risk has been emphasised in many studies (Ebrahim et al., 1995; Mallon et al., 2002; Orth-Gomér et al., 1993; Rosengren et al., 1989; Verbrugge & Balaban, 1989).

It has been suggested that non-married people, whether divorced, widowed, separated or never married, have in general more health problems and higher mortality rates compared with people who are married (Berkman, 1988; Reisine, 1993). The relationship between marital status and mortality is not well understood. Ward and Leigh (1993) found that unmarried people presented with a higher score on the physical function disability index of the HAQ, compared to those married. These results are consistent with those of other studies, suggesting that marriage is an alternative index for wider social support (Ebrahim et al., 1995; Rosengren et al., 1989; Schoenbach et al., 1986). It is generally accepted by those in health psychology and behavioural medicine that the relationship between social support and health has received a great deal of research attention therefore results are considered reliable (DiMatteo, 2004).

Hypertension (HT): There are many risk factors that are believed to be prevalent in RA, and that may be important contributors to the disease, such as HT and smoking (Panoulas et al., 2008). It has been suggested that one of the most important modifiable risk factors for the development of CVD in the general population is HT (Yusuf et al., 2004). The prevalence of HT is high in patients

with RA, and requires prompt diagnosis and appropriate management (Arthritis Research UK, 2011; Panoulas et al., 2008; Stavropoulos-Kalinoglou et al., 2011). However, Gonzalez et al. (2008) stated that the effect of HT on the development of CVD is the same among patients with RA as those non-RA subjects (Gonzalez et al., 2008). Conversely, the mortality rate attributed to HT among RA patients may be higher because cardiovascular mortality rates are already higher in RA compared to non-RA cases (Gabriel, 2008; Solomon et al., 2003; Wallberg-Jonsson et al., 1997; Wolfe et al., 1994). Panoulas et al. (2008) assert that HT in RA patients should be actively treated with drugs and lifestyle measures, not passive monitoring.

HT was reported in many ways in the medical notes. How it is defined in this study depends on how it was reported, often only that the participants were taking anti-HT.

Smoking: Cigarette smoking has also been suggested as a possible cause of RA and other autoimmune diseases, and needs to be actively discouraged (Hardy et al., 1998; Krishnan et al., 2003). Smoking has by far the strongest association with RA among environmental factors (Tobón et al., 2010). Although some studies suggest that smoking habits may be related to RA severity, the impact of smoking on disease activity and outcomes remains unclear (Manfredsdottir et al., 2006; Papadopoulos et al., 2005; Saag et al., 1997; Wolfe, 2000). Smoking was reported in the medical notes as whether the patients actively smoked or not. A history of previous smoking was not included because of a lack of data reported.

Obesity and body mass index (BMI): In the general population, obesity is regarded as one of the well-established risk factors for developing CVD, HT, diabetes mellitus, gall bladder disease, and some forms of cancer (Bray & Bellanger, 2006). Obesity is common in RA patients (Bray & Bellanger, 2006; Jawaheer et al., 2010; Stavropoulos-Kalinoglou et al., 2011). Most of the studies assessing bodyweight in RA use the WHO definition for overweight and obesity (WHO Consultation, 2000).

Bodyweight is routinely assessed and consistently reported in all health departments (Stavropoulos-Kalinoglou et al., 2011). Nevertheless, it is mainly indicated as a demographic of the population studies and is usually excluded from further analysis or interpretation (Stavropoulos-Kalinoglou et al., 2011). BMI has been used as the measure of obesity for both adults and children (Stavropoulos-Kalinoglou et al., 2011; Zaninotto, 2006). The WHO (WHO, 2000) defined BMI as weight in kilograms divided by the height in meters squared. A normal BMI ranges between 18.5-25kg/m²; less than 18.5kg/m² is regarded as underweight, overweight ranges between 25 and 29.9kg/m², and individuals more than 30kg/m² are regarded as obese (Bray & Bellanger, 2006; Stavropoulos-Kalinoglou et al., 2011; WHO Consultation, 2000). The BMI range is a common tool that assesses obesity at the whole-body level; it takes into account total weight but it does not distinguish between the different tissues that comprise it (Stavropoulos-Kalinoglou et al., 2011). Fat mass and other tissues (skeletal muscle, bone, organs, skin and blood), collectively known as fat-free mass, are components of total weight and can vary enormously between individuals (Mattsson & Thomas, 2006).

Disease Activity: (DAS28): This is one of the common indices used to measure disease activity in RA patients in clinical practice (Aletaha et al., 2005; Prevoo et al., 1995). The score is calculated by including the number of tender and swollen joints (out of a total of 28), the ESR and the patient's own assessment of his/her global health, the latter of which indicates the wellbeing of an individual by marking a 10cm line between very good and very bad (Aletaha et al., 2005; Prevoo et al., 1995).

Since the DAS28 contains reduced joint counts, it can also feasibly be used for the monitoring of RA disease activity in daily clinical practice (Fransen et al., 2003). Many studies have suggested that joint counts consisting of only 28 joints are as valid and reliable as the total joint count in RA patients (Fuchs & Pincus, 1994; Prevoo et al., 1995; Van Riel & Schumacher, 2001). A DAS28 score greater than 5.1 suggests an active disease, less than 3.2 indicates that RA is well controlled, and less than 2.6 means that the disease is in remission status (Aletaha et al., 2005; Prevoo et al., 1995). As part of monitoring and follow up, all rheumatologists and healthcare professionals make a medical record of disease activity for every RA patient at each visit.

Rheumatoid Factor (RF): This is the first autoantibody present in serum and synovial fluid of RA patients (Song & Kang, 2010). It was first described by Waaler who developed the Rose Waaler test (Waaler, 1940). Later on, this factor was developed to be defined as an autoantibody that is activated against the fragment-crystallisable (FC) portion of immunoglobulin G (IgG). Three RF species are available, such as IgG, IgM and IgA, but the commonest and most important is IgM (Nell et al., 2005; Song & Kang, 2010; Waaler, 1940). RF is

present not only in RA but has been observed in many other autoimmune diseases such as systemic lupus erythematosus, mixed connective tissue disease and primary Sjogren Syndrome, as well as in non-autoimmune conditions, such as in chronic infections and old age (Tehirian & Bathon, 2008; Temprano & Smith, 2011; Waaler, 1940).

However, RF in RA is present in high titre, while in other conditions it presents with a low titre (Song & Kang, 2010). It has been suggested that RF plays a role in the pathogenesis of RA because of the strong association between high-titre RF and an unfavourable prognosis of the disease (Song & Kang, 2010). RF is shown to be associated with poor outcome for joint destruction and disability (Nell et al., 2005; Song & Kang, 2010). Presence or absence of RF gives a hint to clinicians about the prognosis of disease process because +ve RF is regarded as one of the main factors of a poor prognosis.

Comorbidity: Other medical conditions sometimes present in addition to RA when associated with the disease process, and its treatments are called comorbidities (Michaud & Wolfe, 2007). Comorbidity can be defined to describe a health condition whether in current, past or transient illness such as interstitial lung disease, asthma, ischaemic heart disease (IHD), myocardial infarction (MI), HT and old TB or previous malignancies (Michaud & Wolfe, 2007). Comorbidities in RA are an important factor for QoL and other outcomes and prognosis; therefore, it is essential to recognise illnesses such as cardiac diseases in order to understand research outcomes (Michaud & Wolfe, 2007). It is the responsibility of the physicians and healthcare professionals to accept and monitor the impact of comorbid conditions (Michaud & Wolfe, 2007). A number of

studies have been published over the past decades reporting disability at work (Barrett et al., 2000; Sokka & Pincus, 2001; Verstappen et al., 2004). During the course of the disease, the percentage of patients that become too disabled to work is high (Verstappen et al., 2004). Long-term disabilities, which interfere with permanent employment, have substantial impact on patients' lives, family income, and indirect costs to society (Young et al., 2002). However, work-related disability in RA may result due to reasons other than the disease: demographic variables and social conditions (Sokka & Pincus, 2005).

There are many studies from the USA and European countries that have reported work disabilities in patients with RA with inconclusive findings (Barrett et al., 2000; Revenson & Felton, 1989; Sokka & Pincus, 2001; Wolfe & Hawley, 1998). This inconsistency/discrepancy might be due to differences in the diagnostic criteria of RA, DD, and follow-up periods, or might also be due to the methods employed for recruiting patients (Barrett et al., 2000). Therefore, it is difficult to make comparisons with these studies.

In this chapter, in addition to patients from study One and Kellgren Centre participants, the results of this study were compared to four hydrotherapy studies (Bilberg et al., 2005; Eversden et al., 2007; Hall et al., 1996; HyDAT Team, 2009), as well as other epidemiological studies in the literature. HyDAT authors are the HyDAT team from the UK. HyDAT is the National Hydrotherapy Data Collection project in aquatic physiotherapy, and is regarded as the first UK standard data collection project that provides an outline of aquatic physiotherapy provision within the NHS (HyDAT Team, 2009). Other outcomes such as BMI, smoking and HT were compared with other RA-related studies. Regarding marital

status and occupational status, there were no available study data with which to compare with the data from this study, therefore these data were compared between Kellgren participants (Study Two) and patients from Study One.

7.2.3 Data management and analysis

The Statistical Package for SPSS19 was used for analysis of the data (Armonk, New York 10504-1722, USA). Means (\pm SD) were calculated for all variables and used to describe the outcomes for the Kellgren Centre and patients from Study One. Data were presented descriptively using bar charts.

Where outcomes were compared using inferential statistics, the Kolmogorov-Smirnov test was used to determine a normally distributed population (Field, 2009). The mean and SD of normally distributed data were calculated and reported (Morgan et al. 2010). Independent parametric and non-parametric tests were used to compare groups where appropriate. Statistical significance was set at $p < 0.05$.

7.3 Results

The aim of this study was to collect data for 10% of 2,000 patients at the Kellgren Centre during routine clinical contacts. The data of 200 participants (51 males and 149 females) were collected during a three-month period in 2011. The study population consists of 200 participants from Kellgren Centre (Study Two) and 43 participants in Study One.

Patient details

Age

From Figure 7.1 (p.207), it can be seen that the highest percentage of age group was elderly patients in the two studies, mainly 61-70 years and then 71-80 years.

This indicates that RA commonly occurs in the elderly age group, concurring with all research results as well as with the literature. The lowest percentage appeared in the younger age group. Patients in the Kellgren group were in greater proportion in all age groups except the lowest and highest (2%, 17%).

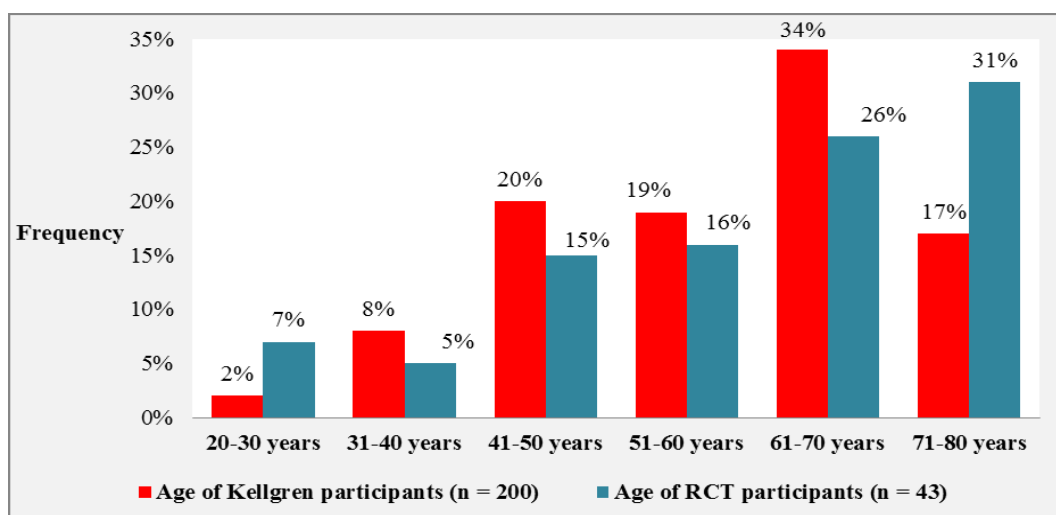


Figure 7.1: Comparison of age groups between participants of Kellgren Study Two and RCT Study One.

Figure 7.2 (p.208) illustrates the main characteristics of the participants' mean age of comparator studies. The mean age was similar between groups, with no difference greater than a few years observed. On average, the mean age was shown to be within the normal range. The mean age of Kellgren participant's was 59 years, which corresponds well with Study One (60).

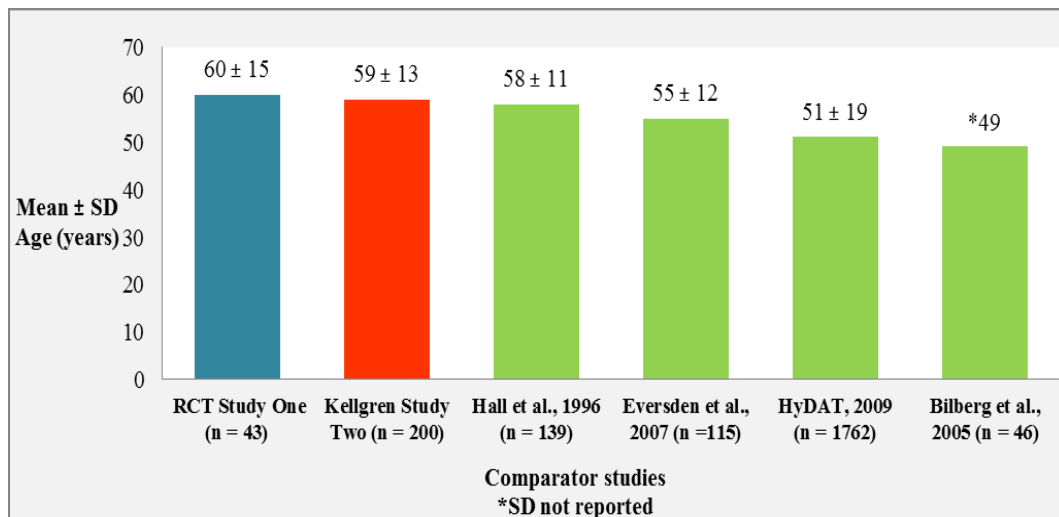


Figure 7.2: Mean (\pm SD) age of six comparator studies.

Occupation

Figure 7.3 shows that 36% of the Kellgren participants were employed, 32% were retired and 1% were students. These findings are comparable with the Study One, which identified (points out) that more than 35% were employed and 49% were retired. Although RA affects older people, it also affects those who are younger and in work at the time of diagnosis. Data were not collected on reasons for retirement because of the difficulty in recording this information and it would have been a great burden on the clinicians.

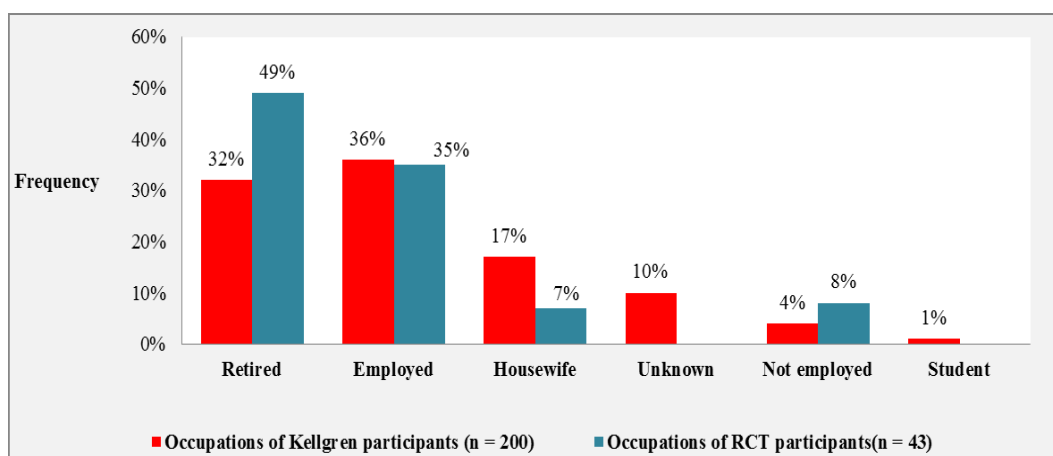


Figure 7.3: Occupational status of participants in both Kellgren Study Two and RCT Study One.

Gender

Figure 7.4 shows that the percentage of females to males in Study One is very similar in the Kellgren Study Two. In comparator studies, the percentage of females ranged from 62% in the HyDAT study to 89% in the Bilberg et al study (2005). Bilberg et al. recruited a very high female percentage of patients (89%) compared to the others. There was a 27% difference between the highest (89%) and lowest (62%) female participation. It is significant that the findings of this study's data concur with that found in the NICE guidelines (2009). The overall occurrence of RA is two to four times greater in women than men (NICE, 2009). Furthermore, Arthritis Research UK, (2011) reported that RA affects women three times more than it does men (Arthritis Research UK, 2011). The percentages of females among Study One participants and Kellgren participants were similar, being three-quarters female compared to one-quarter male.

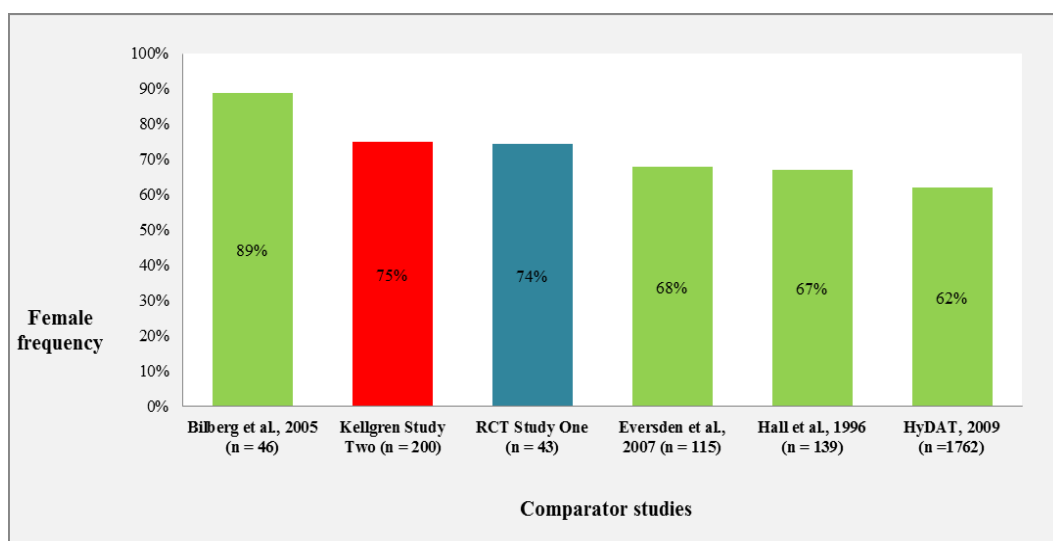


Figure 7.4: The percentage of female patients among six comparator studies.

Disease duration

Figure 7.5 shows that there was little difference in mean DD between the study groups. The only exception is the Bilberg et al. (2005) study that recruited patients with DD between one to five years. In Eversden et al. (2007), the DD of patients ranged between 4 and 18 years, whereas in Hall et al. (1996) it was 7-12 years. Conversely, Kellgren participants' duration of the disease ranged between 1 and 43 years, and the range of Study One participants is 1-50 years.

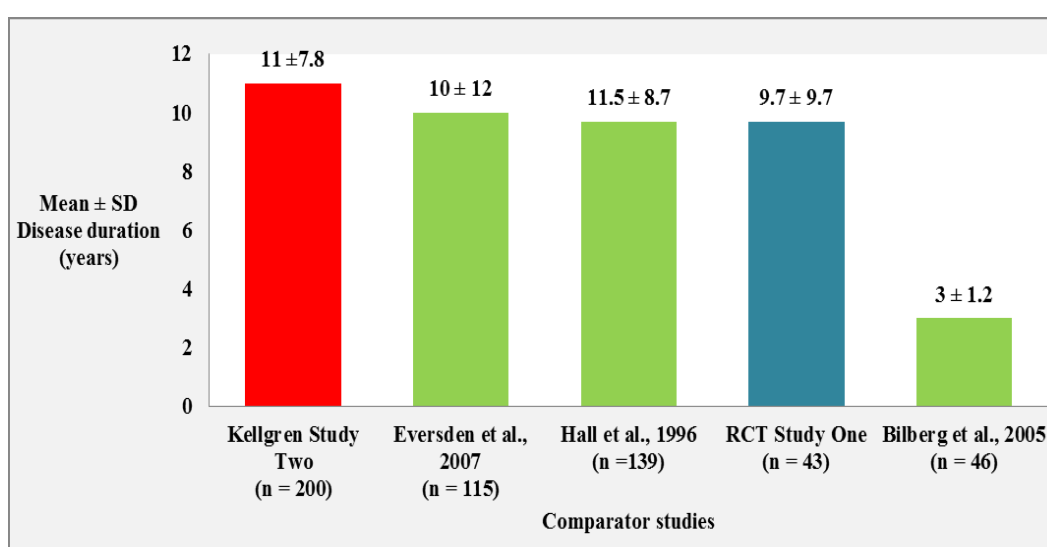


Figure 7.5: Mean (\pm SD) disease duration of RA participants among five comparator studies.

Marital status

With regard to marital status, approximately 65-75% of participants in both the RCT Study One and Kellgren participants were married, compared to 8-19% who were single in both groups (Figure 7.6, p.211). A small percentage of patients (2-11%) presented with other marital status: divorced, widowed or separated. Not all comparator studies reported marital status. Therefore, comparisons between present patients and Kellgren patients were carried out. There were no specific

data found in NICE (2009) or Arthritis Research UK (2011) that could provide any specific marriage data with which to compare.

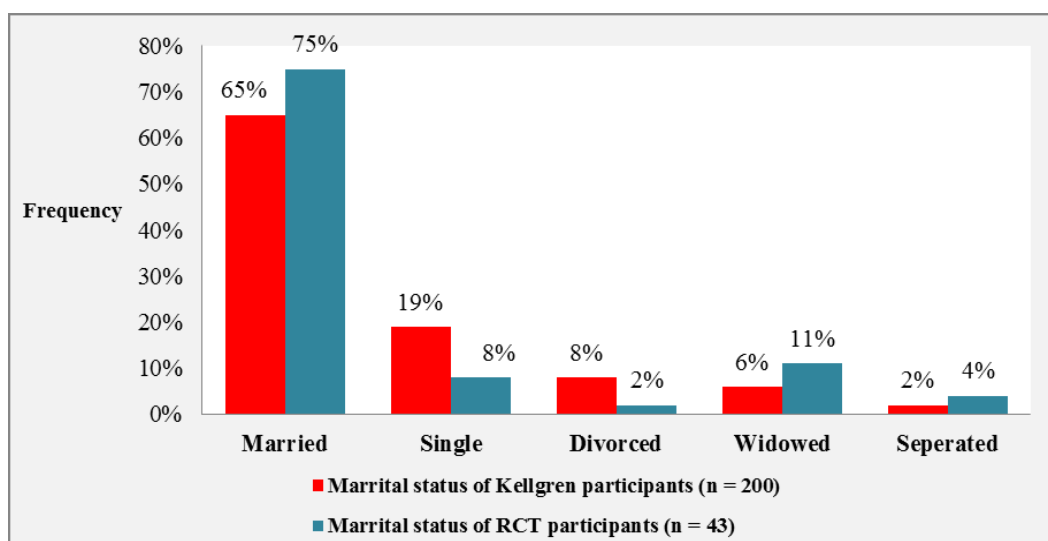


Figure 7.6: Marital status of participants in Kellgren Study Two and RCT Study One.

Body mass index (BMI)

From Figure 7.7, it can be seen that the range of both normal weight and overweight BMI were similar in the two. Very few participants presented with BMI in the underweight range in either of the studies.

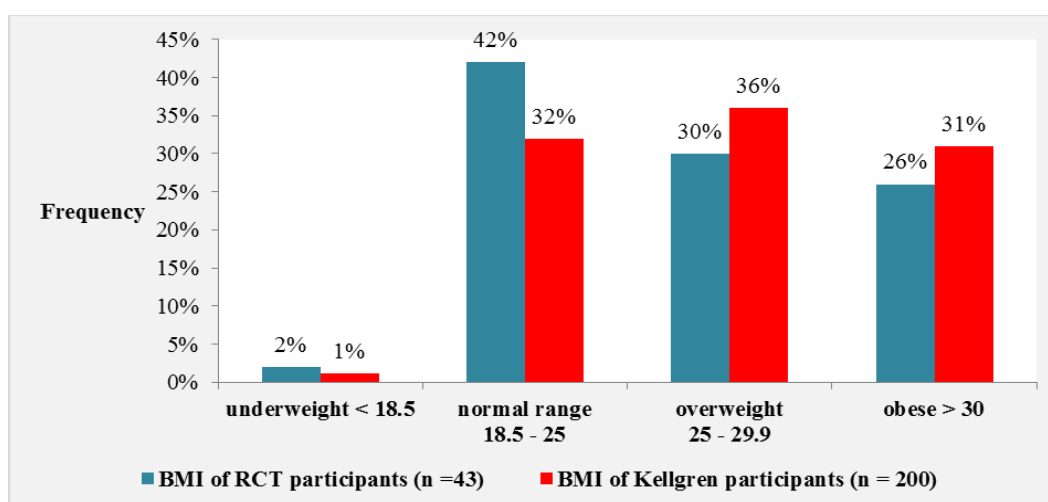


Figure 7.7: BMI index of RA participants in Kellgren Study Two and RCT Study One.

As shown in Figure 7.8, the mean BMI reported for the Kellgren Centre and participants in Study One were similar to the general population in the UK and other RA studies such as Saravana & Gillott, (2004), Stavropoulos-Kalinoglou et al., (2011) and The Information Centre for Health & Social Care, (2011).

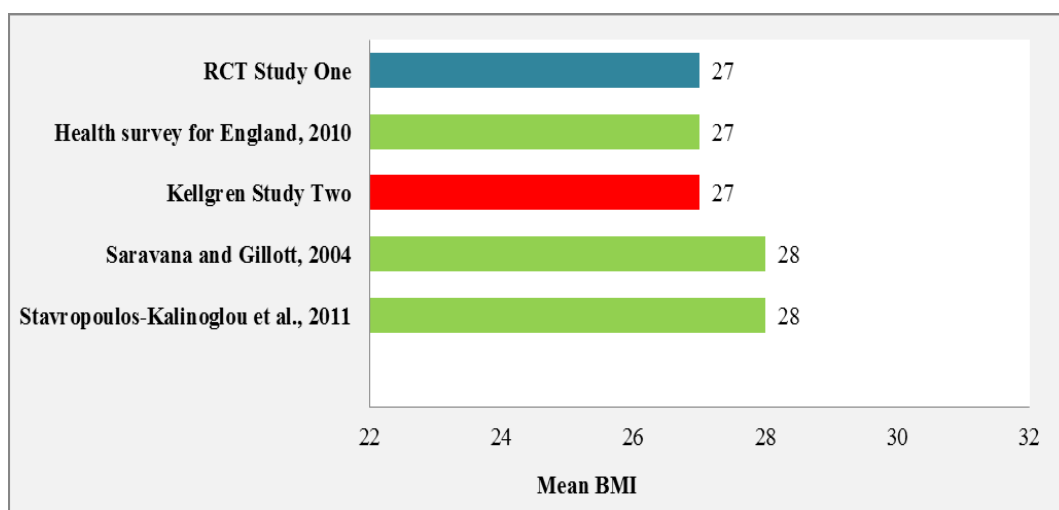


Figure 7.8: Mean BMI index among five comparator studies.

Hypertension (HT)

Figure 7.9 shows the number of RA participants who have HT in both Study One and the Kellgren Centre. 67-70 % of participants in both groups did not have HT.

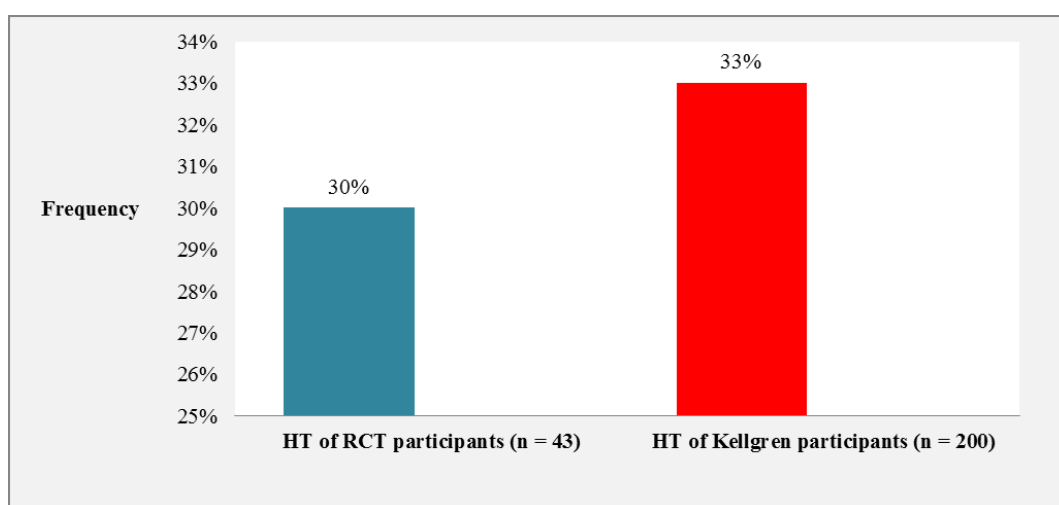


Figure 7.9: Hypertension of RA participants in Kellgren Study Two and RCT Study One.

In Figure 7.10, the prevalence of HT in the general UK population in 2010 was around 30%, and this figure has remained steady over the last seven years, between 2003 and 2010 (The Information Centre for Health and Social Care, 2011). In comparison with other studies, it has been found that the percentage of HT in RA patients varied depending on the studies reviewed.

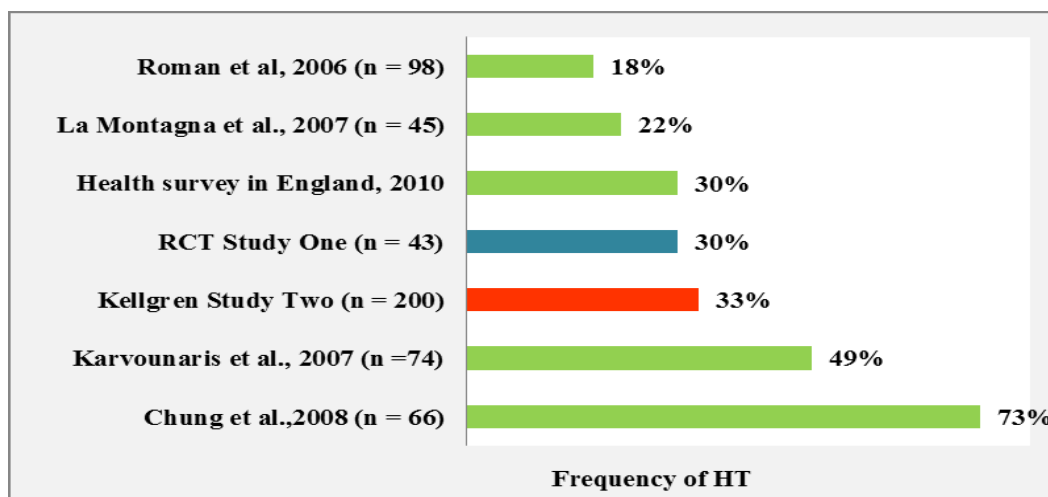


Figure 7.10: Hypertension among seven comparator studies with RA participants.

Smoking

According to the Figure 7.11 (p.214), the percentage of active smoking in the Study One was 12%, while in the Kellgren participants it was 6%. However, other reviewed studies offered a different percentage of participants' smoking habits, beginning at 42% in Hutchinson et al. (2001), 34% in Manfredsdottir et al. (2006), 29% in Papadopoulos et al. (2005) and 27% in Finckh et al. (2004). The health survey data for the general population in England (2011) reported that the percentage of men who were current smokers declined from 28% in 1993 to 22% in 2010, while in women the proportion of current smokers declined from 26% to 18% for the same period (20% altogether in 2010, i.e. the total decline across both genders) (The Information Centre for Health and Social Care, 2011).

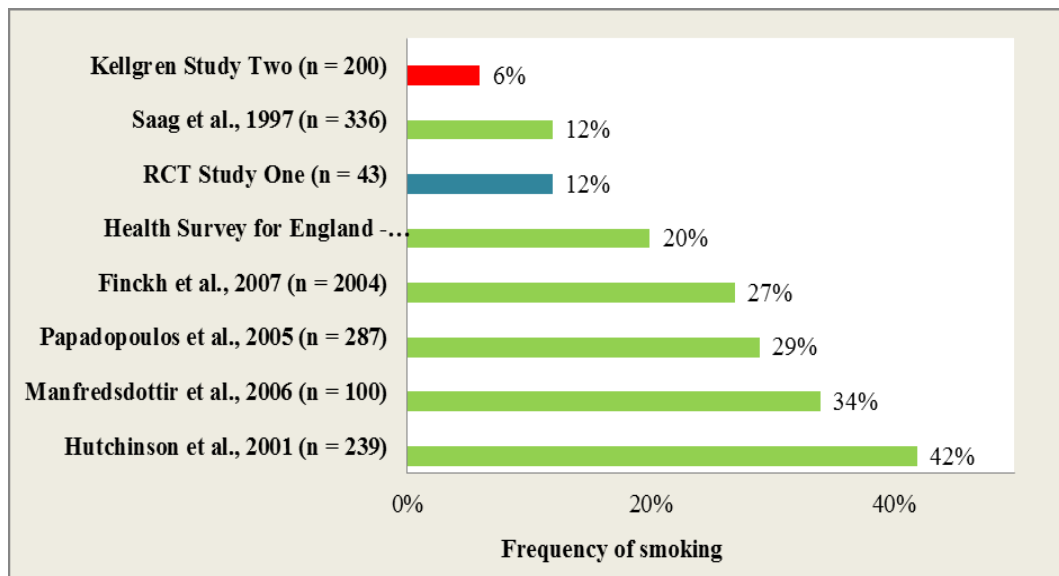


Figure 7.11: Percentage of smokers in study populations.

DAS28

In both groups most participants had a DAS28 score of between 3.2 (well controlled) and 5.1 (exacerbation of disease activity), which was double the percentage of those who had a DAS28 score of less than 2.6 (remission of disease activity) (Figure 7.12).

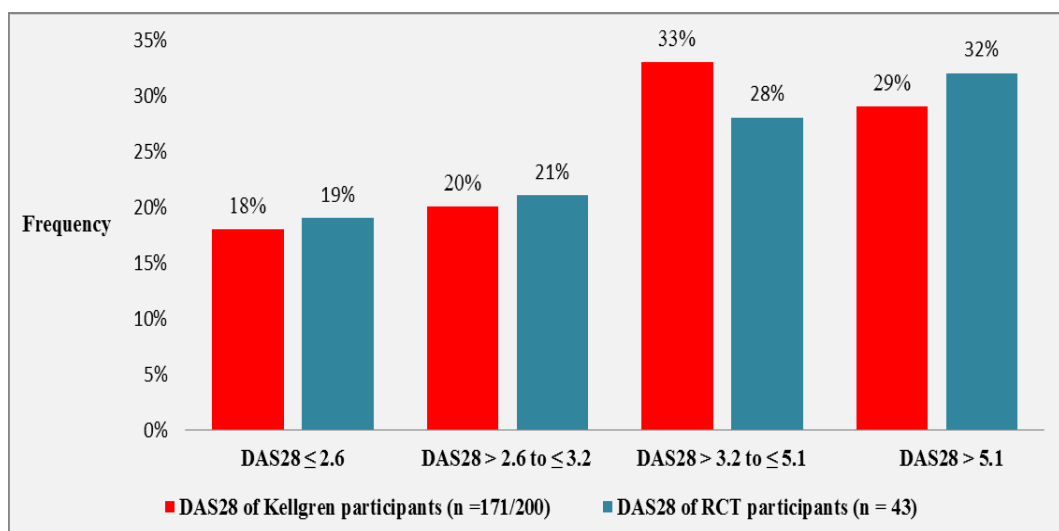


Figure 7.12: DAS28 among RA participants in the Kellgren Study Two and RCT Study One.

Comparisons of DAS28 scores between the Kellgren Study Two and the RCT Study One were made using independent t-tests because the DAS28 baseline score was normally distributed ($p = 0.075$). The mean (\pm SD) Kellgren DAS28 score was $4.1 (\pm 1.5)$ compared to $4.3 (\pm 1.7)$ in the RCT Study. This was not statistically significant ($p = 0.845$) (Figure 7.13).

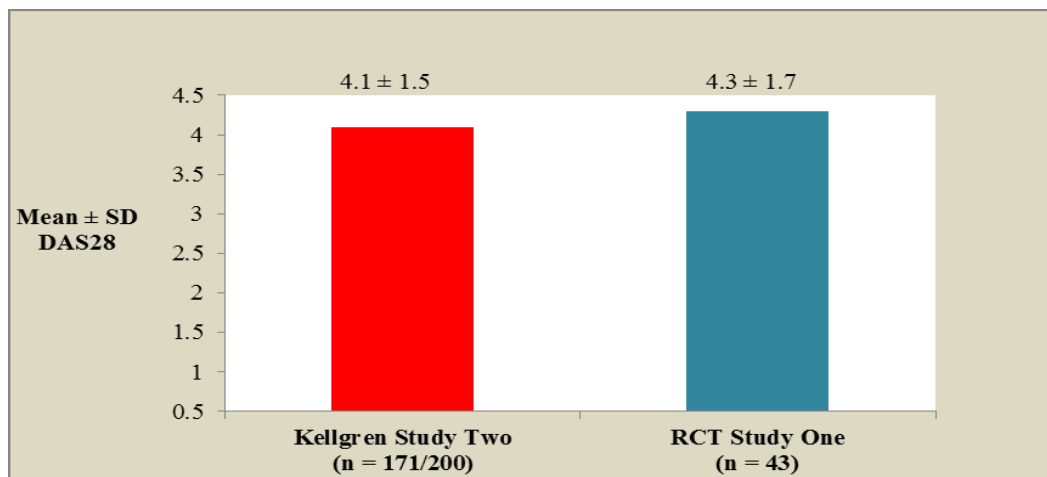


Figure 7.13: Mean DAS28 between RCT Study One and Kellgren Study Two.

Rheumatoid factor (RF)

Figure 7.14 (p.216) illustrates the percentage of participants who had positive RF. It can be seen from Figure 7.14 that more than 44% of Kellgren Study Two participants had +ve RF compared to 63% in the RCT Study One. The majority of participants in Rantapaa-Dahlqvist et al. (2003) have positive RF (73%) compared to 45% in Nell et al. (2005).

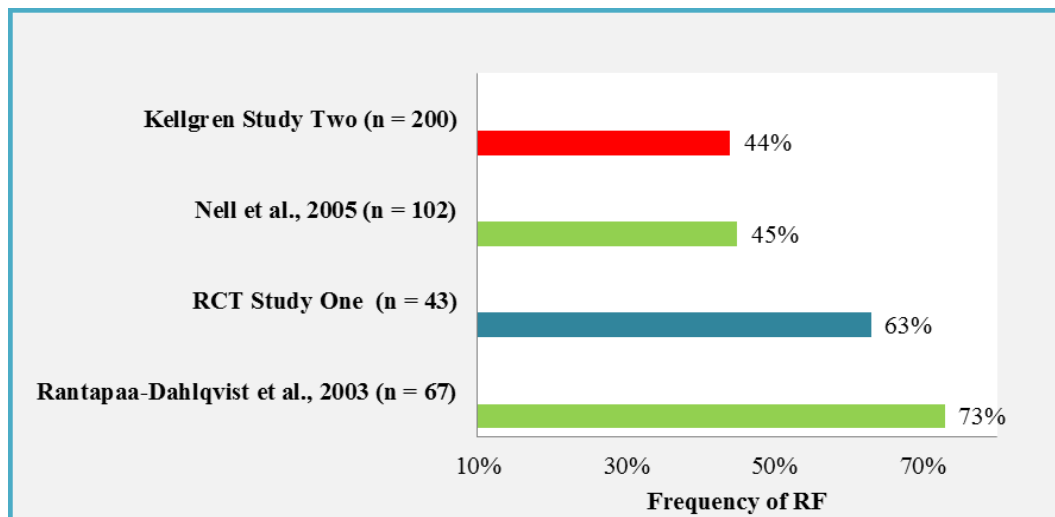


Figure 7.14: Proportion of Rheumatoid factor positive in RA participants among four studies.

Treatment details

Figure 7.15 (p.217) shows that the most common medications used in all RA populations among the studies reviewed were DMARDs and NSAIDs. Only Hall et al. (1996) found that more patients were taking NSAIDs than DMARDs. In the RCT study and the Kellgren Centre, biologics were used to treat RA patients. From Figure 7.15, it can be seen that 14% of Study One participants were on biologic drugs compared to 28% in the Kellgren Centre. None of the hydrotherapy studies reported any data about biologic drugs.

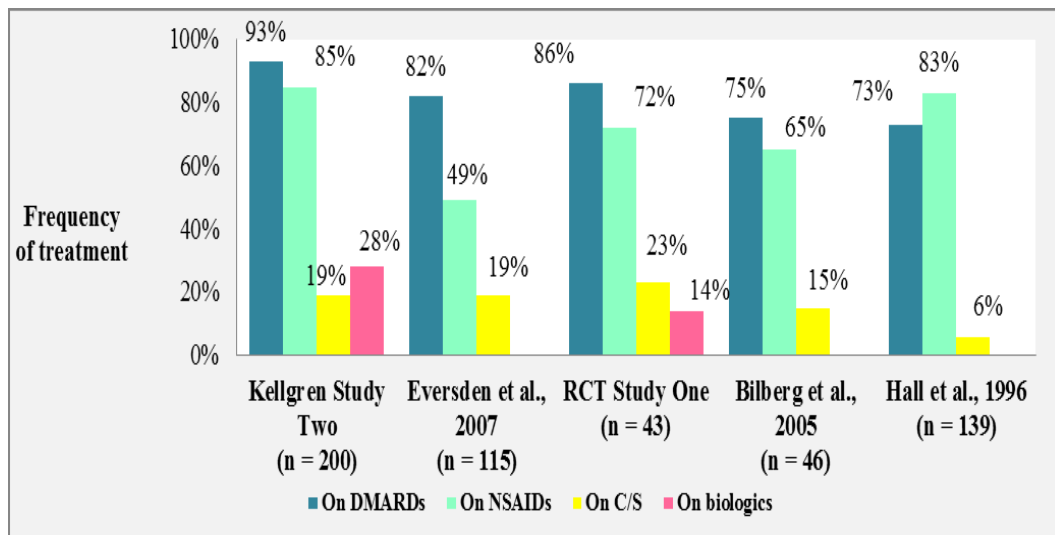


Figure 7.15: Treatment details of five comparator studies among RA participants.

Comorbidities

Figure 7.16 illustrates the commonest types of illnesses associated with RA in the Kellgren Study and the RCT Study. The interesting findings were that 40% of Study One and 33% of Kellgren participants did not have comorbidities. Both groups have various illnesses to be taken into consideration during rehabilitation.

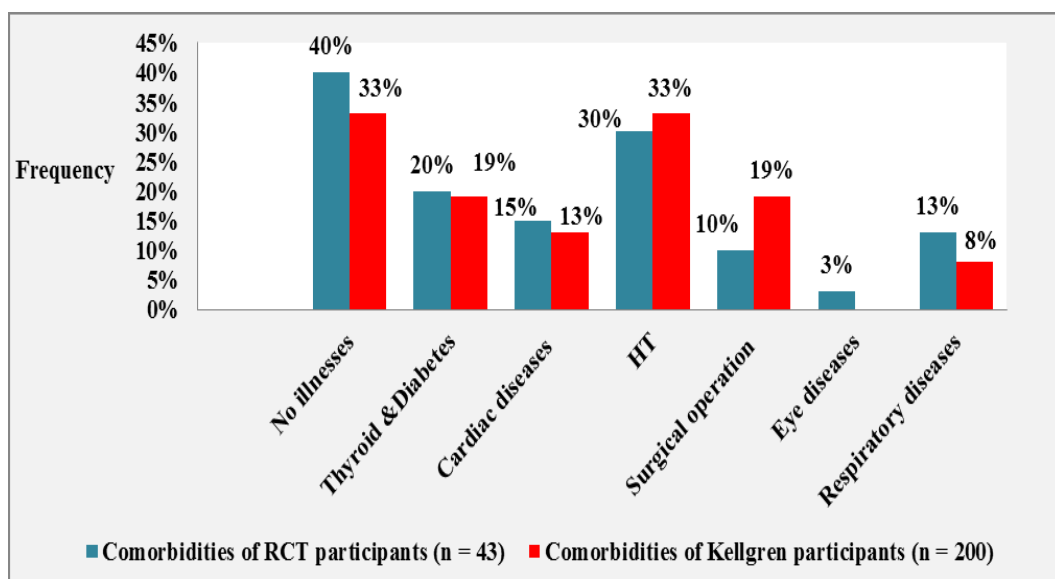


Figure 7.16: Comorbidities of RA participants in Kellgren Study Two and RCT Study One.

7.4 Limitation of Study Two

In general, most of these data were commonly available in the clinical notes. Unfortunately, not all the participants' medical notes contained full data. Because the data was collected by the research nurse and entered onto a form in writing, it relied on her interpretation of the notes and our interpretation of her writing. Numbers and words not clearly written could have been interpreted differently by another person reading the same notes.

We accepted a margin of error of 7.1% as defined by Niles, (2006). A larger sample would have decreased the margin of error, possibly leading to different findings. However, a balance needed to be struck between feasibility and margin of error accepted.

An initial attempt was made to find additional outcomes such as early environmental factors, birth weight, pollutant exposure, and laboratory tests such as anti-CCP; these items were not typically reported however, and future research would have to collect this information specifically.

Few studies have attempted to explain the effects of several environmental factors on the risk and outcome of RA, such as environmental factors that might affect RA many years before its clinical occurrence (Mandl et al., 2009; Silman & Pearson, 2002; Tobón et al., 2010). Early environmental factors such as growth or lack of it and diet are regarded as high in the risk of developing RA (Tobón et al., 2010). A large cohort study in USA followed 87,077 women prospectively as part of the Nurses' Health Study, and they have considered the positive relationship

between high birth weight (> 4.54kg) and RA compared to no relation to normal birth weight (Mandl et al., 2009).

The relationship between pollutants and RA has been also investigated. The established link between air pollution and diseases involving pulmonary and systemic inflammation such as asthma and chronic bronchitis indirectly support this hypothesis (Tobón et al., 2010). Recent evidence suggests that a newly identified environmental risk factor for RA may be exposure to traffic pollution in adulthood (Hart et al., 2009). A recent study used in the Nurse's Health Study (90,297 women) examined the distance between the place of residence in 2000 and the nearest road, which served as an indicator of exposure to traffic pollution (Hart et al., 2009). What is interesting in this data is that women living within 50m of a road radius had an increased risk of RA compared to women living 200m or more from the road radius (Hart et al., 2009). However, it could not be concluded without further evidence that this data could be confirmed.

A relationship exists between some ethnic and racial groups and their incidence of a higher risk for RA than others (Tobón et al., 2010). The differences in the distribution and interactions of genetic and environmental factors might be related to this high risk.

7.5 General findings

- The mean age of the Kellgren Study Two and the RCT Study One participants was 60 years. This finding was comparable to what Arthritis Research UK (2011), NICE (2009) and other studies have reported.

- All comparator studies have reported that RA affects more women than men.
- The DD between Kellgren and RCT Study was similar, which reflects the RA population who have been referred to hydrotherapy.
- Most participants from the Kellgren Centre and in Study One were either in employment or retired. A higher proportion referred to hydrotherapy were retired.
- Both studies reported that more than 55% of RA patients were overweight or obese, and these findings were comparable with other literature studies.
- All studies that were reviewed had approximately similar mean BMI scores.
- Variable percentages of smoking were reported among comparison studies. However, very low percentages of smokers were reported in both the Kellgren Study and the RCT Study.
- A very wide range of HT prevalence has been reported between literature studies.
- Several literature studies have reported variable percentages of RF in their studies.
- No significant differences were shown between the DAS28 of the Kellgren study and RCT study.
- Biologics drugs were reported only in the RCT Study and the Kellgren Study. No literature studies reported information about biologics drugs. However, biologics drugs have only recently been introduced for treatment of RA patients, and this might explain the reasons for no data having been

reported among comparator studies. The trends of drug medication were almost the same in the Kellgren Study Two and RCT Study One.

- A number of comorbidities were reported in both Kellgren Study Two and Study One participants.

The following chapter will discuss the results of economic evaluation (Study Three) of hydrotherapy modality for the RA patients compared to the land-therapy group from the perspectives of the provider, society and the patient.

CHAPTER EIGHT: AN ASSESSMENT OF HYDROTHERAPY COSTS TO THE NATIONAL HEALTH SERVICE (NHS), PATIENTS AND SOCIETY COMPARED WITH LAND-BASED EXERCISE THERAPY (STUDY THREE)

8.1 Introduction

Although clinical outcomes are important, they are not the only outcomes considered and applied by clinicians and policy makers in the evaluation of effectiveness treatment in healthcare (Bozic et al., 2003; Cohen & Reynolds, 2008). It is due to the considerable rise in the cost of healthcare and the increase in restraints on economic resources that decision-makers have been caused to consider re-evaluating healthcare in terms of cost (Cohen & Reynolds, 2008; Donaldson et al., 2002). Decision-makers now aim at increasing the welfare of patients up to a given level equal to the allocation of resources. Thus, the combination of economic evaluation with clinical trials in order to evaluate effectiveness requires an economic analysis-shaped decision-making framework that can be used by clinicians, managers and policy makers (Goodwin et al., 2003). In developing countries, the financial constraints of care are increasingly important for economic and political issues (Cohen & Reynolds, 2008). It has been realised that new medical products and technologies are one fundamental driver of increased healthcare costs (Goldman et al., 2005). This recognition has increasingly highlighted the need to assess the value of new methods of strategies

to discover the effects of tests, drugs, procedures, and medical devices relative to their costs (Cohen & Reynolds, 2008). Therefore, the analysis of CE should also include the evaluation of such problems (effect vs. cost) in order to inform clinicians (medical decision) and healthcare policy-makers.

Over several decades, the discipline of CE analysis has developed as an approach to accurately assessing the value of new medical strategies by concurrently examining incremental health benefits in light of incremental costs (Cohen & Reynolds, 2008). Originally, the design of this study was a cost-effective analysis to determine the clinical and cost-effectiveness of hydrotherapy compared to land-based exercise therapy in RA patients. However, it is accepted that it is impossible to specify the technique of analysis in advance when arranging a prospective economic evaluation (Donaldson et al., 1996; Donaldson et al., 2002; Drummond et al., 1997). Among individuals with musculoskeletal conditions it has been stated that arthritis, such as RA and OA, are regarded as a first- or second-rank cause of long-term disability, work disability, restricted activity days, frequent medical visits, and prescription and non-prescription drug use (Patrick et al., 2001; Rothfuss et al., 1997). Intuitively, it may be easily predicted that providing an average of six sessions of hydrotherapy exercise by the NHS is more costly than land therapy (because the costs of hydrotherapy are higher than those on land). Those patients attending hydrotherapy impose more costs on healthcare than land sessions. Nevertheless, it should be appreciated that provision of hydrotherapy may reduce the NHS costs (which can be called the hidden costs). The lack of hydrotherapy sessions in a hospital can increase the cost to the NHS.

The patients who receive hydrotherapy cost less in the end than their counterparts who do not get treatment, and because of the reduction in hidden costs, this can also be claimed to be true for those receiving land-based treatments.

This chapter is a cost analysis, examining the cost of providing hydrotherapy sessions compared to providing land-therapy sessions, where the effectiveness of both treatments has not proven to be equal, as in the HAQ-DI. The study considers the cost of the treatment from the viewpoint of healthcare providers, patients and society, in view of the limited health resources available. Decision-makers choose the treatment strategies they want to implement in the context of the lowest cost per QALY (Detsky & Naglie, 1990; Tengs, 2004).

Cost utility is measured in QALYs divided by the incremental cost, and it is defined as the ratio of the incremental effectiveness of one strategy, such as hydrotherapy, compared to another, such as land therapy (Epps et al., 2005; Fenwick et al., 2006; Gusi & Tomas-Carus, 2008; Willan, 2001). Studies reported in the literature have demonstrated evidence of the benefits of physiotherapy on HRQoL in RA patients, such as reducing pain and increasing fitness from short-term programmes (Eversden et al., 2007; Hall et al., 1996; Rintala et al., 1996). However, the cost-analysis evaluation of these exercise programmes in RA patients is not readily available. It is important that the CE of a health service – which takes into account not only the perspective of the healthcare provider but also of the patients themselves, and society – is added to the evaluations; particularly in terms of the time spent on treatment, travel, and lost work hours.

These factors give decision-makers necessary information that will help them to provide the best possible healthcare within the limited resources allocated to them.

Aim of Study Three

The aim of this chapter was to evaluate the cost of hydrotherapy compared to the land-based treatment, from the viewpoint of the provider [NHS], patient and society.

8.2 Rationale for undertaking a cost analysis study

Arthritis such as RA and OA is the leading cause of disability among USA populations older than 15 years, and is regarded as the second most prevalent cause for work disability (Wing & Peterson, 2012). It has been stated that the economic cost of arthritis in the USA in 2003 was about \$108 billion annually (Yelin et al., 2007). The total costs of RA in the UK including indirect costs and work-related disability have been estimated at between £3.8 and £4.75 billion per year, and these costs include NHS costs, career costs, nursing home care, private expenditure, sick leave and work-related disability (NICE, 2009; The Comptroller and Auditor General, 2009). The wider cost to the general economy due to sick leave and work-related disability (lost employment) is £1.8 billion a year (NICE, 2009). It has been found that about one third of patients have to give up work because of the disease within two years of its onset, and this prevalence increases thereafter (James et al., 2004; NICE, 2009). A survey by the National RA Society estimated that when a patient stops work due to RA it represents an average loss of productivity equivalent to £287,544 (NICE, 2009). Undoubtedly, this disease represents a huge cost to the UK economy and an enormous cost to individual

patients (NICE, 2010); it can therefore be accepted that RA results in a wide range of complications for the individual patient, their carers, the NHS and society in general (NICE, 2010).

The economic impact of this disease includes (NICE, 2009):

- Direct cost to the NHS with their associated healthcare support services.
- Indirect costs to the economy in terms of the effects of early mortality and lost productivity.
- Personal impact on patients and their families because of disease and subsequent complications.

RA is a chronic and progressive disease for which there is no cure at present, necessitating complex treatment. The aims of hydrotherapy treatment in rheumatic diseases are to sustain or improve functional mobility and independence (Eversden et al., 2007; Fam, 1991; Rintala et al., 1996). Clinical trials have shown that exercise programmes, whether on land/or in water, might be helpful in relieving pain, increasing functional ability and improving depression due to the fact that these programmes increase strength and ROM in affected joints (Hall et al., 1996; Rintala et al., 1996; Suomi & Collier, 2003; Templeton et al., 1996; Vliet Vlieland & Van den Ende, 2011). Hydrotherapy is an accepted form of treatment administered in concurrence with usual care therapy and other physiotherapy rehabilitation programmes, such as land-based exercise and home exercise. Generally, RA patients are satisfied with the hydrotherapy services that are recommended by NICE guidelines for the management of this chronic disease (Epps et al., 2005; HyDAT Team, 2009; NICE, 2009).

Because of the chronicity of RA, any intervention that minimises deformity and disability without the use of drugs must be considered over prescribing drugs, which tend to have side effects that are significant due to the longevity of the disease. Although it can be seen through this study that the costs of hydrotherapy are higher than those of land-based physiotherapy treatment, costs may be neutralised against efficiency gains if less staff time is required with individual patients, and fewer drugs and resources are needed to support the development and functioning of the RA patients. The hypothesis is that hydrotherapy will be more costly than land-based physiotherapy in the treatment of RA patients, but that it will give more benefits in terms of pain relief, less disabilities and a better QoL.

8.3 Economic evaluation: a review

8.3.1 Materials and methods

8.3.1.1 Identification and selection criteria

An electronic database search of AMED, CINAHL, the Cochrane Library, EMBASE, MEDLINE, ProQuest, Pub Med, Science Direct, and the Web of Science was conducted (1988 to September 2013). The search was limited to human adults (age >18 years) and across all articles published in English. The keywords used were 'rheumatoid arthritis', 'hydrotherapy', 'aquatic physiotherapy', 'aqua therapy', 'water therapy', 'costs', 'cost evaluation', 'economic evaluation', 'cost utility', 'cost effectiveness'. Keyword combinations were: 'rheumatoid arthritis and hydrotherapy', 'rheumatoid arthritis and aquatic physiotherapy', 'rheumatoid arthritis and aqua therapy', 'rheumatoid arthritis and

water therapy', 'rheumatoid arthritis and costs', rheumatoid arthritis and cost evaluation'.

Studies that used the following keywords were excluded from this literature search: 'colonic irrigation', 'water birth', 'Kneipp therapy', 'spa therapy', 'whirlpool therapy', 'contrast baths' and 'balneotherapy'. The database search was supplemented by a manual search of: the Clinical Journal of Rheumatology, Annals of the Rheumatic Disease, British Medical Journal, Physiotherapy, Arthritis and Rheumatism, Rheumatology and Journal of Rheumatology and Physical therapy. A further search of the bibliographic references in the extracted articles and existing reviews was also conducted to identify potential studies that were not captured by the electronic database searches.

This section identifies and summarises the economic evidence from RCTs in rheumatic diseases similar to RA, evaluating the use of hydrotherapy (aquatic exercise, pool therapy) in RA patients. From consequences of RCTs, the best economic evaluations are determined. In clinical outcomes, comprehensive costing can be undertaken to ascertain the true costs associated with the observed improvement in results if a well-designed RCT establishes a difference (Doig, 2008). Few studies have included economic evaluations in rheumatic diseases, but they have included patients with juvenile idiopathic arthritis (JIA), FMS and osteoarthritis (OA) (Cochrane et al., 2005; Epps et al., 2005; Gusi & Tomas-Carus, 2008; Patrick et al., 2001).

8.3.1.2 Inclusion and exclusion criteria for considering studies for this review

Studies were included if:

- They were RCTs;
- They included participants in any age group who had been diagnosed with RA, JRA, OA, FMS and AS;
- A water-based intervention (hydrotherapy) had been used in the study, and compared with alternative interventions;
- They included an economic evaluation.

Articles were excluded if:

- They had insufficient information available (abstract only);
- The treatment modality included balneotherapy, Kneipp therapy, mud therapy or sulphur therapy;
- They were not written in English (even if the abstract was in English);
- Participants were not primarily and predominantly diagnosed with common rheumatic disease.

From the search, four articles were identified based on economic evaluations of hydrotherapy in OA, FMS and JIA upon RCTs named (Cochrane et al., 2005; Epps et al., 2005; Gusi & Tomas-Carus, 2008; Patrick et al., 2001).

Patrick et al. (2001) recruited 249 adults diagnosed with OA using a stratified randomisation process in order to estimate cost and outcomes of the Arthritis Foundation's 20-week aquatic exercise classes from a societal perspective. Participants in the treatment group took part in an Arthritis Foundation-certified

aquatic class, and class size ranged from six to 40 persons with an average of 16. This aquatic programme was run by practiced instructors and held in pools with a temperature of 85°F to 92°F.

Participants performed gentle upper- and lower-body activities to help increase joint flexibility and ROM and maintain muscle strength. Participants were asked to attend classes at least twice weekly for the 20-week study period. Participants in the control group were withheld from new exercise programmes for the duration of the study and were asked to follow their usual pattern of activities. QALY gained was estimated using trial data. Sample size was based on 80% power to reject the null hypothesis that the cost/QALY gained would not exceed \$50,000. The economic evaluation, the QWB – a generic measure of health status – was used in the Patrick et al. (2001) study to estimate cost utility (CE) analysis with a community-derived preference weighting (Kaplan & Anderson, 1988). This outcome measure was previously used in evaluating Auranofin medication in RA (Thompson et al., 1988). Additional outcome measures collected at baseline and post-class included the Current Health Desirability Rating (CHDR) scale; this was used with participants, who were asked to rate the desirability of current health (Tsevat et al., 1995), the arthritis-specific Health Assessment Questionnaire (HAQ) (Fries et al., 1980; Fries et al., 1982), the Centre for Epidemiologic Studies-Depression Scale (CES-D) (Kohout et al., 1993), and the Perceived Quality of Life Scale (PQoL) (Patrick et al., 1988; Patrick et al., 2000).

To estimate costs, the use of healthcare facilities was assessed using diaries/questionnaires and Medicare reimbursement rates. Based on the observed

extents of clinical benefit, the authors calculated the CE of hydrotherapy for arthritis to be in excess of USD \$50,000 per additional QALY gained, and considered this prohibitively expensive. The outcome measures were taken immediately after the finishing intervention and did not allow any analysis of longer-term effects; nevertheless, this trial was regarded as having high methodological quality (Epps et al., 2005). This study did not determine reduced costs and improved health outcomes compared with usual care. As a result the incremental cost-utility of the exercise programme (using the QWB community-derived preference weighting) was not favourable compared with other common healthcare interventions (such as usual care) because the QWB was not sensitive enough to detect a significant difference with the sample size used (Patrick et al., 2001). Conversely, preference weights obtained using the participant-specific CHDR improved significantly in the exercise group. Consequently, the cost-utility outcome of the aquatics exercise programme using the CHDR was more favourable.

Cochrane et al. (2005) in the UK performed a subgroup economic evaluation. A pre-experimental matched-control study (106 participants) was used to estimate efficacy of water-based exercise treatment of over 12 weeks to check design assumptions and delivery processes. This was followed by the main study of 312 participants in an RCT to determine the effectiveness of water-based exercise (treatment) compared with usual care (control) in older patients with hip and/or knee OA.

The main study by Cochrane et al. (2005) was accompanied by an economic evaluation comparing societal costs and consequences of the two treatments. A subgroup analysis of this trial focussed on the incremental CE in patients older than 60 with hip and/or knee OA. One hundred and six elderly patients (93 women, 13 men) with confirmed hip and/or knee OA took part in the preliminary study.

CE was evaluated from the incremental cost-effectiveness ratios (ICERs – difference in mean cost divided by difference in mean effect in the two groups). Primary analysis was performed on an intention-to-treat basis, with last available measurement carried forward. Mean cost difference estimates showed a saving in the water-exercise group of £123–£175 per patient per annum, and ICERs ranged from £3,838 to £5,951 per QALY.

The water-exercise programme produced a favourable cost-benefit outcome, using reduction in pain score on the Western Ontario and McMaster Universities (WOMAC) OA index as the measure of benefit. Wide variation in both the individual costs and the utility measures, combined with small effect sizes, limited the power of the study to detect a difference between the groups on QALY-based analyses, so for this reason, the overall cost of this programme may be prohibitively expensive.

Gusi and Tomas-Carus (2008) assessed the cost utility of adding an eight-month supervised warm-water exercise programme to the usual care of public health

service for women with FMS. Costs to the healthcare system and to society were considered in this study.

The participants in this trial were randomly allocated using a random-number table and assigned a code number. After excluding five participants due to their participation in other therapies, 33 female patients aged 37 to 71 years of age were selected to participate. Seventeen participants were allocated to the experimental group, consisting of a one-hour session three times weekly for an eight-month duration. The remaining 16, who continued their daily activities (which did not include any form of physical exercise similar to that in the programme) were allocated to a control group. Provision was made for additional costs that are variable among patients, such as the cost and time needed for travel from the patient's residence to the hospital. This facility is unusual in health services. For this reason, the authors achieved two economic analyses, one from a health-service perspective, the other from a societal perspective, to assess the costs to the patient and to the provider.

The unit costs were expressed in Euros (€) based on prices in 2005. The main outcome measures used were the healthcare costs and the number of QALYs using the time trade-off elicitation technique from the EQ-5D utility (Drummond et al., 1997; Herdman et al., 2001). At the beginning of the programme and after three and eight months, participants completed the questionnaires, including the EQ-5D health status instrument (Drummond et al., 1997; Herdman et al., 2001). Private and public healthcare was recorded, during the same period, including hospital stays, drug usage and primary and secondary care appointments.

Gusi and Tomas-Carus (2008) showed that the mean incremental treatment costs exceeded those for usual care per patient by €517 from a healthcare-provider perspective, and €1,032 from a societal perspective. Each QALY gained in association with the exercise programme cost an additional €3,947/QALY (95% CI: 1,782 to 47,000) from a healthcare perspective, and €7,878/QALY (3,559 to 93,818) from a societal perspective. Again, the addition of the water-based programme is potentially prohibitive per QALY in terms of both healthcare and societal costs. Before investing in such programmes, many factors need to be considered as a major determinant, such as characteristic facilities (distance from patients' homes and number of patients in each session).

In the UK, Epps et al. (2005) conducted a clinical trial in JIA that was commissioned by the NHS Research & Development Health Technology Assessment (HTA) Programme. This trial was designed as a multicentre randomised controlled, partially blinded trial. Two-hundred participants were randomly allocated into an intervention arm receiving a combination of hydrotherapy and land-based physiotherapy (combined group) compared to a control arm receiving land-based physiotherapy only (land-therapy group). Patients in both groups received 16 sessions (one hour/session) of treatment at one of the three centres over two weeks, followed by local physiotherapy attendances for two months. The inclusion criteria were: patients aged four to 19 years diagnosed more than three months previously with JIA, on stable medication with at least one active joint.

They were recruited from three centres in the UK. Costs per QALY gained at six months following the main intervention were calculated using a societal framework to reflect costs to society. This included calculating the hours of paid or unpaid work lost because of the patient's illness. For example, a carer or their partner might have to stay at home to look after a child who has a disease flare, or take them to hospital or physiotherapy appointments. QALYs were derived using the EQ-5D (Drummond et al., 1997; EuroQol Group, 1990; Herdman et al., 2001). The measurement and calculation of costs and QALYs are described below.

Two months after intervention 47% patients in the combined group and 61% patients in the land-therapy group had improved according to the EQ-5D scale, whereas 11% and 5% worsened, respectively. The analysis showed no significant differences in mean costs and QALYs between the two groups. It was not possible to carry out a sample size calculation relating to the exact context of this trial, as there was no firm evidence as to the proportion of patients with JIA likely to improve in the control arm of the study (Epps et al., 2005). Another explanation might be because there are no studies in this age group used for comparison to help resolve some of the findings of this trial. Moreover, the EQ-5D may not be responsive to real change in the paediatric population because it was not designed to measure children's health status (Epps et al., 2005).

It would appear from the studies discussed above that an economic analysis was not intended to be a major component, except in the study of Gusi and Tomas-Carus (2008). A clear perspective was not stated in three of the reviewed studies (Cochrane et al., 2005; Epps et al., 2005; Patrick et al., 2001). The cost elements

of these studies should be considered with caution as they fall short of the recommendation proposed for a full analysis of costs, as well as due to the inconclusive findings, small sample sizes and lack of applicability to patients with RA (Drummond et al., 2005). Providing research for policy makers, which is intended to influence health-service provision, should include wide-ranging measurement of outcomes, and consideration of costs at the outlay (Kernick, 2000).

8.4 Methods of cost measuring & outcomes for economic analysis

Because the resource is not available for its best alternative use, the appraisal principle used was the economic concept of opportunity cost, that is, the value of the foregone benefit (Drummond et al., 2005; Drummond et al., 1997). Opportunity cost is established on the basis that resources are rare, thus, every time resources are used in one way, the opportunity of using them in another way is removed. From an NHS perspective, the opportunity cost of using scarce resources to treat RA patients is the benefit. This might have been obtained from their best alternative use, for example the treatment of other patients with neurological and musculoskeletal injuries (Drummond et al., 2005; Drummond et al., 1997; Goodwin & Morrissey, 2003). Moreover, when considering costs incurred by patients, the opportunity costs are also important. It is believed that at the point of consumption, patients incur null costs because in a healthcare system the services are free (Ratcliffe et al., 1996). However, patients may be incurring costs because patients attending physiotherapy may incur travelling or childcare costs, or may forego income.

It has also been suggested that while some desirable interventions such as hydrotherapy may not modify life expectancy, they may provide remission and relieving effects and thus improve QoL, whereas others may meaningfully change both the quantity and QoL. Therefore, the cost-utility analyses are recommended, with QALYs serving as the preferred measure of effectiveness (Cohen & Reynolds, 2008; Gold et al., 1996). The costs to society and cost per QALY gained at six weeks following the main intervention were calculated because experts encourage the use of QALYs in cost utility studies mainly across a wide variety of health conditions such as RA (Cohen & Reynolds, 2008). From a societal perspective, the travelling time and time spent at the patient's appointment has an alternative use – in the form of paid or unpaid work lost (work time or leisure time lost) as a consequence of the patient's illness, for example the patient may be a student or homemaker, or a carer may have to stay in the home because of disease flare, hospital appointments for physicians or physiotherapists.

This study estimated the incremental mean costs of the hydrotherapy programme, and the mean QALY was added to the programme from the perspectives of the healthcare provider, the patients and society. Costs were referred to as direct medical (NHS), direct non-medical (patient) and indirect (societal) costs. Due to the difficulties of their measurement and valuation, insubstantial costs in the form of pain and anxiety, related to the effect of receiving or not receiving treatment, have not been considered in this analysis (Goodwin et al., 2003).

There are two methods of using QALY in the cost utility analysis. The standard method that is strongly recommended in economic theory is through directly

eliciting utilities from patients. Unfortunately, this method is difficult to apply practically in the UK for ethical reasons and because it is time consuming (Cohen & Reynolds, 2008; Gusi & Tomas-Carus, 2008; Torrance, 1986). The second method, which is more often used and called the 'indirect method', is where patients complete a generic health survey such as the EQ-5D (EuroQol Group, 1990; Rabin et al., 2011a) or Short-Form 36 (Ware & Sherbourne, 1992).

The cost utility analysis used the EQ-5D score (utility or tariff – see chapter 5, section 5.2.4.2, p.146) to calculate mean health-state values (plus measure of variance) of patients in the hydrotherapy group and land-therapy group at Test 1 and Test 2. These scores were converted to QALYs. Estimates of mean costs and QALYs six weeks post-intervention were calculated (Epps et al., 2005). It is important to mention that total costs and QALYs remain undiscounted because the analysis was less than one year in duration. In this chapter, the costs included only the treatment patients actually received, irrespective of allocation or intended number of treatments, for which reason intervention-treatment sessions were recorded (Epps et al., 2005). Figure 8.1 (p.240) shows a schematic process of the points during the study, the cost data was collected.

8.4.1 Direct medical (NHS) costs

All these costs occurred within the healthcare sector relating to the provision of patient treatment, such as:

- Staffing costs (physiotherapists, GP, physicians and consultants' time);
- Departmental costs (allocated overheads);
- Medication (for example, prescribed by the GP/consultant);

- Other procedures (further surgery, examination, rehabilitation);
- Equipment (allocation of fixed costs).

Staffing time: Calculations of staffing time costs included the physiotherapist and assistant once a week for six weeks in the hydrotherapy group, and for the physiotherapist only in the land-therapy group. At the follow-up test, data were collected using questionnaires (Appendix 31) to determine the number of visits made to a GP or alternative therapist. Information on the cost of these visits to the patient was also collected after the six-week intervention period. General Practitioners' (GP) time was calculated from an average surgery consultation of 11.7 minutes (Curtis, 2011) and then multiplied by the number of visits made. The number of visits to the consultant rheumatologist was determined from the patient's medical notes.

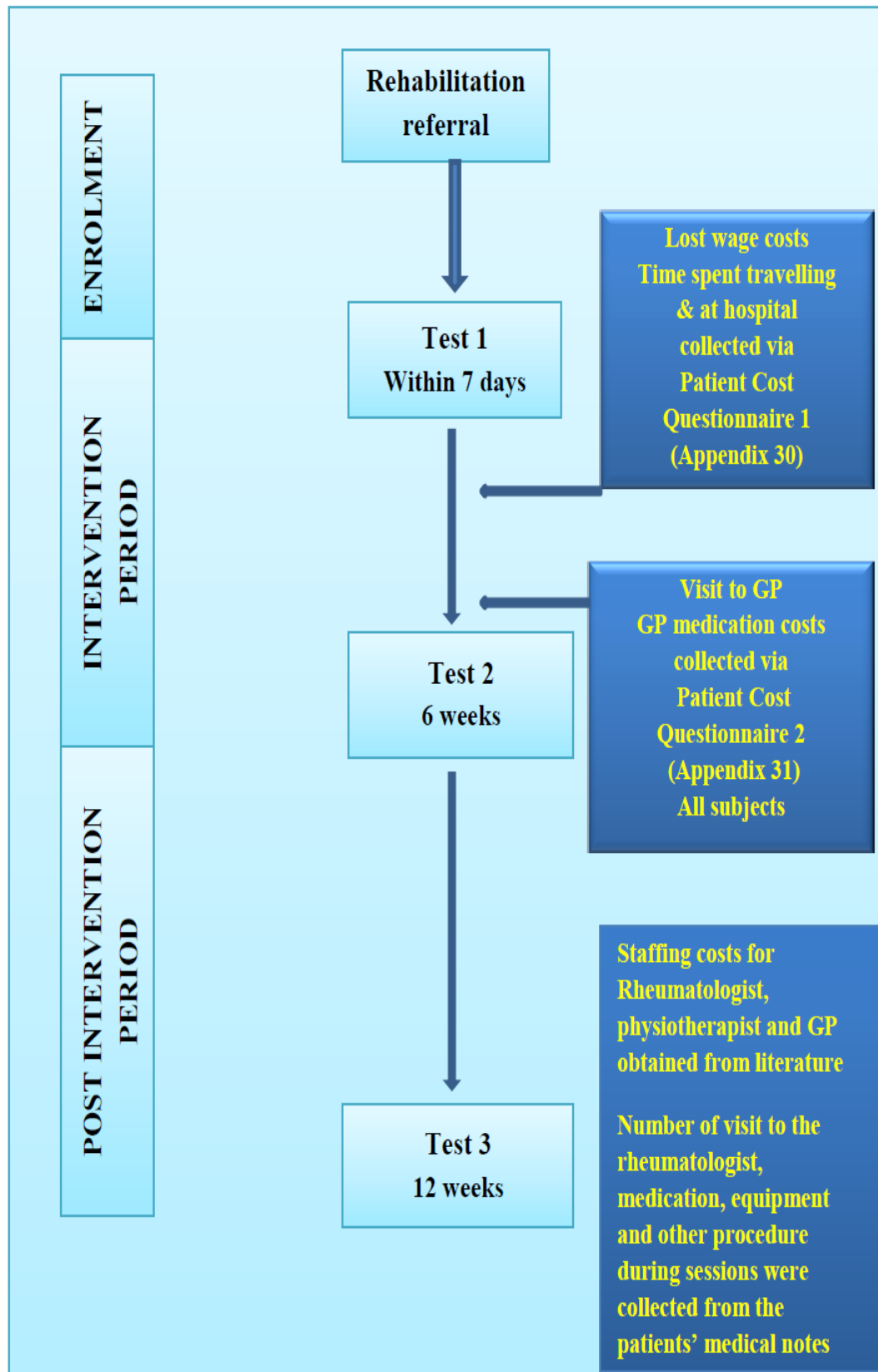


Figure 8.1: Schematic processes for collecting data.

Staffing costs: these were calculated using the average wage rate (AWR) for GPs and physiotherapists (Table 8.1, p.242) (Curtis, 2011). GP costs were calculated using expected income for a full-time GP and an average surgery consultation time of 11.7 minutes and average cost of £36 per visit. The sum included practice expenses, qualifications, ongoing training, capital costs and overheads. Consultant rheumatologist costs were taken as the unit cost of a hospital medical outpatient attendance. Costs included the total net revenue expenditure for this service. For physiotherapists, costs were calculated based on the median full-time equivalent of a Band 5 clinician (Curtis, 2011) (Appendix 32). For assistants, costs were calculated based on the median full-time equivalent of a Band 3 Allied Health professional support worker (Curtis, 2011) (Appendix 33). Median full-time equivalent total earnings included basic salary plus hours-related pay, overtime, occupation payments, location payments, and other payments such as redundancy pay or payment of notice periods (Curtis, 2011).

The sum included salary on costs, qualifications, indirect and capital overheads and training. An example of the unit estimation is taken from Curtis (2011) and shown in (Appendix 32). These data were applied from the NHS Reference Costs (Department of Health, 2011). Where subjects indicated that a visit to the GP had been made but no cost was incurred, it was supposed that no medication was prescribed. No cost to the NHS could be assumed as all of the subjects indicated that they were exempt from prescription charges (unemployed; over retirement age, full-time students under 19 and medical exemptions). Information regarding

medication prescribed by the consultant rheumatologists was obtained from the medical notes.

Table 8.1: Key unit costs used to value resource use measured during the trial (prices = GBP £).

Item	Unit	Cost (£)
GP (Curtis, 2011)	Per visit	36.00
Consultant (medical) (Curtis, 2011)	Per hour	89.40
Physiotherapist (Curtis, 2011)	Per 45min session	24.00
Physiotherapy assistant (Curtis, 2011)	Per 45min session	18.00
AWR for male employer (Curtis, 2011)	Per hour	8.70
AWR for female employer (Curtis, 2011)	Per hour	7.77
AWR for housework and leisure time (Curtis, 2011)	Per hour	4.46
Car usage (The Automobile Association Limited, 2011)	Per mile	0.44
Key: AWR: Average wage rate GP: GP Min: minutes		

Equipment Costs: During the physiotherapy treatment, these were calculated and expressed as the annual equivalent cost (Drummond et al., 2005; Drummond et al., 1997). The annual cost is based on a standardised 3.5% interest rate with an assumed life expectancy of equipment of five years, with an alternative assumption of 10 years (Building Cost Information Service, 2011; Curtis, 2011). The equipment purchased was used in the hydrotherapy pool for the treatment of all patients with variable diseases, therefore the capital outlay was a shared cost as patients with other injuries such as neurological disease or sports injuries were able to benefit from its use. The annual equivalent cost was apportioned to reflect

the time it was in use by these patients. Table 8.2 (p.244) shows the price of equipment, which was obtained from the 2012 catalogue for hydrotherapy and land-based therapy in the UK (JPLennard Ltd, 2012)¹. Equivalent annual cost of equipment lasting more than one year was calculated, such as chlorination machine and gym-based equipment. The formula used to calculate the annual equivalent cost was (Drummond et al., 2005; Drummond et al., 1997):

$$K = E / (1 - (1 + R)^{-n}) / r$$

Where:

K = Capital outlay

E = Equivalent annual cost

r = Discount rate (interest) 3.5%

n = Useful life of equipment

¹ UK, Swift Point, Rugby, CV21 1PX

Table 8.2: Price of hydrotherapy and land-exercise equipment (adapted from JPLennard Ltd, 2012).

Equipment	Unit per annum	Unit cost (£)	Annual equivalent cost (+VAT)* (£)
Hydrotherapy consumables			
Woggle	6	5.9	35.40
Ankle floats	4	5.52	22.08
Ring	4	6.7	26.80
Fins	1	12.49	12.49
Paddles	1	10.5	10.50
C collar	1	10.84	10.84
Blocks	1	39.93	39.93
Gloves	4	7.87	31.48
Overshoes	100 pairs	£8/50 pairs	16.00
Chlorine tablets	2	12.95	25.90
Maintenance	1	2300	2300.00
Sodium hypochlorate	4	35.9	143.60
Polyalum chloride	4	39.13	156.52
Sodium bicarbonate	4	41.25	165.00
Thyosulphate flakes	4	36.75	147.00
Sodium biosulphate	4	32.62	130.48
Delivery	4	55	220.00
Plumbers	1	147	147.00
Capital items			
Chlorination machine*	1	520	337.35
Hydrotherapy Total			£3978
Land equipment			
Arm weights	1	20.76	20.76
Floor Mat	3	18.75	56.25
Exercise bike	2	260	520.00
Land Total*			£434
Total			£4.412

*Annuitised 3.5*10 years

8.4.2 Direct non-medical costs

Direct non-medical costs are those foregone by the patient, family, or partner in the pursuit of treatment, such as out-of pocket expenses, including:

- Travel costs (patients, family, or partner);
- Lost wages (patients, family, or partner);
- Prescriptions costs;
- Other costs.

Travel costs: This describes all modes of travel to the hospital including car, bus, train, taxi, ambulance, walking and other such as Metrolink. Tickets on public transport were taken as the reported cost of a two-way ticket to the hospital. The cost of these journeys was doubled when accompanied by a companion who did not also have an appointment at the hospital. Car usage cost was determined at 44 pence per mile based on a petrol car costing up to £12000 travelling an average of 10,000 miles per year, including standing charges and running costs (The Automobile Association Limited, 2011). It was presumed that a car journey shared with a companion who also had an appointment at hospital halved the cost of that journey. Travel costs were excluded from any companions without appointments travelling by car, and walkers and cyclists incurred no travel costs on their journey (Goodwin et al., 2003). Parking fees were taken as the actual amount reported, and travel costs were not included if the subject was eligible for reimbursement. Lastly, we accounted for all journeys that included different modes of transport or involved one mode of transport to the hospital and a dissimilar one on return.

Lost wages: These were included as out-of-pocket expenses only if the subject responded as taking ‘time off with loss of pay’ whilst attending physiotherapy. The out-of-pocket expense was taken as the AWR (£8.70 for males, £7.77 for

females) (PayScale, 2012). The AWR was substituted with the actual amount of pay lost, where it was reported.

Prescription charges: Those resulting from GP visits were taken as the amount reported in the cost questionnaire (Appendix 31). If costs were omitted, but medication was prescribed, then the average cost of visiting a GP surgery was assumed. If medication was prescribed during a visit to the consulting rheumatologist, the average cost of attending a hospital outpatient appointment was assumed.

Other costs: Those incurred whilst attending the physiotherapy appointment, extra to travel or medical costs, were gained from answers to a general question (Appendix 30) ‘Were there any other costs involved in visiting the hospital today which has not been covered above?’.

8.4.3 Indirect costs

Because of attending physiotherapy for hydrotherapy sessions, the lost productivity of a patient or family member or partner were the main indirect costs to be accounted. The rest of society tolerates these costs. Such costs include:

- Value of time (travel and time spent at hospital).
- Time lost from usual activities foregone, which could be: time lost from work or from non-working activities.

The value of time: This refers to the cost to the patient of the time foregone attending the physiotherapy appointment. Two aspects of time are considered and obtained from questions two and nine in Appendix 30:

- **Travel time;**
- **Time spent at the hospital.**

To rate **the time lost from usual activities foregone**, data were collected on the opportunities forgone, that is, the activity subjects (and their companions) would have participated in had they not attended physiotherapy.

Determining **the usual activity forgone** was by questionnaire (Appendix 30). Subjects were asked to indicate ‘what they (and their companion) would normally have been doing had they not had to visit the hospital’. The difference in the activity forgone is determined because savings in working time are of value to society as a whole, whereas savings in leisure or non-working time only benefit the individual.

Subjects who would have otherwise been in ‘paid employment’ during their appointment were asked; ‘what arrangements they had made to be absent from work’. **The value of time lost at the employer’s cost** was the AWR raised by 21.2% to reflect employers’ National Insurance and superannuation contributions (Department for Transport/Transport Analysis Guidance (TAG), 2011). This included those who responded as having ‘time off with pay’ whilst attending physiotherapy (Appendix 30).

The **value of time lost to non-working activities** was calculated for respondents who ‘arranged annual leave’, ‘rearranged their hours’, ‘would otherwise be looking after children, other relatives, or friends’, or who responded ‘other’. For those who would have otherwise been doing housework, the value of time was £4.46. For those who would have otherwise had leisure or non-working time, the value of time was £4.46 (Department for Transport/Transport Analysis Guidance (TAG), 2011).

8.5 Data analysis

Unit costs were taken from a variety of sources. To give a total cost per patient, the quantities of each resource used were multiplied by fixed unit-cost values and then summed up over the separate types of resources. Comparisons between groups were achieved using Levene’s test (for equality of variances) and the independent t-test. The t-test on untransformed data is the only test appropriate for costs, because it addresses a comparison of the arithmetic means (Thompson & Barber, 2000).

To guide healthcare policy decision-making, a total annual budget is the relevant information required to provide a treatment at a specific hospital. An estimate of this total cost is obtained by multiplying the arithmetic mean cost of a particular treatment by the total number of patients (Thompson & Barber, 2000). Differences were determined statistically significant if the probability was less than 0.05.

8.6 Sensitivity analysis

The number of participants treated per session was varied from one to four for both groups. By varying the number of patients treated at any one time, uncertainty around these results was dealt with using sensitivity analysis.

8.7 Results

Thirty-six (11 males and 25 females) out of 43 participants completed the cost questionnaire two weeks post-treatment. Therefore, the cost analysis was based on these data.

8.7.1 The cost of staff

8.7.1.1 NHS costs

There was a significant difference ($p = < 0.001$) in the total NHS staffing cost per patient between the two groups. The mean total staffing cost per patient was £263 in the hydrotherapy group compared to £145 in the land-therapy group (Table 8.3, p.250). No participants indicated visiting their consultant during the intervention period, and GP costs were the same for the two groups. The biggest difference was in physiotherapy staffing costs.

Table 8.3: The total NHS staffing costs of treating RA patients in the hydrotherapy and land-therapy groups.

	Total NHS staffing costs (£) Mean \pm SD (Range)		
	Hydrotherapy group (n = 19)	Land group (n = 17)	p value (95% CI)
Physiotherapist	252 \pm 0 (252 to 252)	135 \pm 28 (48 to 144)	< 0.001 (-132 to -103)
GP	11 \pm 29 (0 to 108)	10 \pm 27 (0 to 108)	0.936 (-19 to 20)
Consultant rheumatologists	0	0	N/A
Total	263 \pm 29 (252 to 360)	145 \pm 42 (48 to 252)	< 0.001 (-143 to -94)
Significant p values are indicated in boldface Key: N/A: Not applicable			

Because of the size of hydrotherapy pools [7.4 m²] it is possible to treat more than one patient at a time. At the two sites included in this study, it was usual to treat four patients at a time. Treating four patients at a time over six sessions, the total cost to the physiotherapy department per patient was £63 (Table 8.4, 251) meaning that the total staffing costs to the NHS would be £66 instead of £263, making hydrotherapy significantly cheaper. Treating four patients at a time on land would also reduce costs, however this is not normal clinical practice.

Table 8.4: Physiotherapy staffing costs over an average of six sessions in two groups, varied for the number of RA patients treated.

	Total physiotherapy staffing costs in the hydrotherapy group (£)			Total physiotherapy staffing costs in the land group (£)			
Ratio of patients	Mean	SD	Range	Mean	SD	Range	p value (95% CI)
1:1	263	29	252 to 360	145	42	48 to 252	< 0.001 (94 to 148)
2:2	132	15	126 to 180	72	21	24 to 72	< 0.001 (-47 to -2)
3:3	88	10	84 to 120	48	14	16 to 84	< 0.001 (31 to 48)
4:4	66	7	63 to 90	34	7	12 to 36	< 0.001 (57 to 86)
4:1	66	7	63 to 90	145	42	48 to 252	< 0.001 (-101 to -57)
Significant p values are indicated in boldface							
Key:							
SD: Standard deviation							

Patients in both groups reported visiting their GP during the intervention period with no statistically significant difference between the two. In the hydrotherapy group, three subjects (15.7%) visited their GP a total of six times compared to three subjects (17.6%) in the land-therapy group visiting a total of five times (Table 8.5, p.252). No subjects in the hydrotherapy group reported prescriptions for medication during GP visits, whereas the land-therapy group reported an average cost of £3.

Table 8.5: Total medication and GP visitor cost to patient for the hydrotherapy and land-therapy groups after intervention.

	Total NHS medication and procedure Costs (£)						p value (95% CI)
	Hydrotherapy group (n=19)			Land-therapy group (n= 17)			
	n	Mean number of visits	Mean ± SD (Range)	n	Mean number of visits	Mean ± SD (Range)	
GP	3	2	11 ± 29 (0 to 108)	3	1.6	10 ± 27 (0 to 108)	0.936 (-18 to 20)
Medication	0	0	0	1	1	3 ± 13 (0 to 55)	0.332 (-10 to3.6)
Total	2		11 ± 29 (0 to 108)	2.6		13 ± 40 (0 to 108)	0.835 (-26 to 21)
Key:							
SD: Standard deviation							

The annual equivalent cost of hydrotherapy equipment was calculated as £4.412, which was based on a ten-year life span. The cost of equipment for a 45-minute session cost the NHS £10 for one patient, £5 for two, £3.3 for three and £2.5 for four patients compared to £0.06 for treating one patient on land.

The total cost to the NHS of treating one patient for an average of six sessions in hydrotherapy was £325 compared to £148 on land (Table 8.6, p.253). When applying a real-world situation, the total cost of four patients treated at the same time in the hydrotherapy pool was £83 compared to treating one patient on the land, which was £148 – a saving of £65 (95% CI: -90 to -41; $p < 0.001$) (Table 8.6, p.253).

Table 8.6: Comparison of total NHS costs between the hydrotherapy and land-therapy groups over an average of six sessions in two groups, varied for the number of RA patients treated.

	Total NHS cost in hydrotherapy (£)	Total NHS cost in land-therapy group (£)	
Patients per class	Mean ± SD (Range)	Mean ± SD (Range)	p value (95% CI)
1	325 ± 29.5 (314 to 422)	148 ± 52 (48 to 307)	< 0.001 (149 to 205)
2	162 ± 15 (157 to 211)	74 ± 26 (24 to 154)	< 0.001 (74 to 103)
3	108 ± 10 (105 to 141)	49 ± 17 (16 to 102)	< 0.001 (50 to 68)
4	83 ± 9 (78 to 105)	37 ± 13 (12 to 77)	< 0.001 (38 to 53)
4*	83 ± 9 (78 to 105)	148 ± 52 (48 to 307)	< 0.001 (-90 to -41)
*Compared four patients in the pool with one on land Significant p values are indicated in boldface Key: SD: Standard deviation			

8.7.1.2 Patient cost

8.7.1.2.1 Direct non-medical costs

The characteristic transport data are shown in (Table 8.7, p.255). Moreover, Figure 8.2 (p.254) showed work status of participants in both groups.

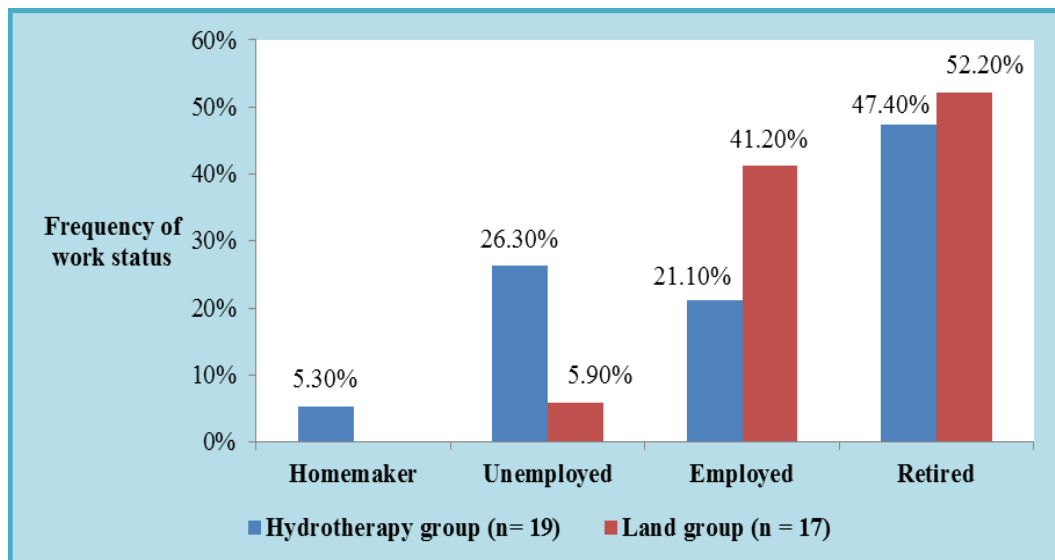


Figure 8.2: Work status of participants in both groups.

In both groups, the average return distance travelled to hospital to attend physiotherapy was similar (hydrotherapy group = 13 miles; land-therapy group = 14 miles). The majority of participants in both groups travelled to and from the hospital by car. One patient in the hydrotherapy group came by taxi. One patient in the land-therapy group walked to all hospital appointments. The mean total cost of travelling to and from physiotherapy for those in the hydrotherapy group was £41, compared to £25 for those in the land-therapy group. This difference was not statistically significant ($p = 0.219$) (Table 8.8, p.256). One patient in the land-therapy group was eligible for reimbursement of travel costs by their employer. In both groups, the average return distance travelled to hospital to attend physiotherapy was similar.

Table 8.7: Transport characteristics in both the hydrotherapy and land-therapy groups, with the number of users in brackets.

	Hydrotherapy group n = 19	Land-therapy group n = 17
Return travel distance (miles)	13	14
Parking car fees (£)	4.5	2
Taxi cost (£)	11 (1/19)	----
Method of transport		
Car	73.7% (14/19)	76.4% (13/17)
Bus or train	10.4% (2/19)	11.8% (2/17)
Taxi 2	5.3% (1/19)	----
Walk	-----	11.8% (2/17)
Ambulance	5.3% (1/19)	----
Other 3	5.3% (1/19)	----
Reimbursement		
Yes	-----	5.9% (1/17)
No	100% (19/19)	94.1% (16/17)
Companions		
Yes	31.6% (6/19)	35.3 (6/17)
No	68.4 (13/19)	64.7 (11/17)

Table 8.8 (p.256) shows the total average out-of-pocket expenses incurred by patients in both the hydrotherapy and land-therapy groups. In total, the hydrotherapy group spent approximately £52 per patient compared to the land-therapy group, who spent £45. This difference was not significant ($p = 0.794$). One patient in the land-therapy group attended two sessions of occupational therapy, and one patient in the hydrotherapy group attended six sessions of acupuncture. No participants in the hydrotherapy group reported any wages lost or

² Taxi cost for only one patient in each visit

³ Other in the hydrotherapy group refers to the Metrolink (Tram Network)

prescription charges. However, one person reported lost wages and two persons reported prescription charges in the land-therapy group.

Table 8.8: Patient out-of-pocket expenses incurred during the six-week intervention period for the hydrotherapy and land-therapy groups.

	Out of-pocket expenses per patient (£) Mean \pm SD (Range)		
	Hydrotherapy group n = 19	Land-therapy group n = 17	p value (95% CI)
Travel to physiotherapy	41 \pm 50 (0 to 219)	25 \pm 20 (0 to 65)	0.219 (-10 to 42)
Lost earnings whilst at physiotherapy	0	17 \pm 72 (0 to 300)	N/A
Prescription charges	0	2.5 \pm 7.5 (0 to 29)	N/A
Other ⁴	11 \pm 48 (0 to 210)	0.50 \pm 1.50 (0 to 6)	0.368 (-13 to 35)
Total (£)	52 \pm 68 (0 to 253)	45 \pm 78.7 (0 to 336)	0.794 (-43 to 54)
Key: SD: Standard deviation N/A: Not applicable			

8.7.1.2.2 Indirect costs

Patients spent a similar amount of time travelling and at the hospital, whether they were attending hydrotherapy or physiotherapy on land. In the hydrotherapy group, the mean **time lost travelling** to the hospital over the course of the six weeks was 64 \pm 44 (range = 20 to 200) min. The mean **time lost at the hospital** attending physiotherapy, including waiting time was 58 \pm 28 (range = 30 to 120) minutes. Therefore, the mean total time lost was 120 minutes \pm 57 (range = 50 to 250)

⁴ Acupuncture in the hydrotherapy group and occupational therapy in the land-therapy group

minutes and the cost would be zero because no participants mentioned any wage lost during travelling (Table 8.9, p.259).

In the land-therapy group, **time lost travelling** to the hospital over the course of the six weeks was 48 ± 23 (range = 20 to 90) min. The mean **time lost at the hospital** attending physiotherapy, including waiting time, was 61 ± 34 (range = 30 to 150) min. Consequently, the mean total time lost was 110 ± 45 (range = 50 to 190) min and the cost would be $\pounds 17 \pm 30$ (range 4 to 133) because only one participant in the land-therapy group lost wages; approximately $\pounds 300$ for six sessions of land therapy.

Figure 8.3 (p.258) shows the usual activities performed, had patients not had to visit the hospital, between two groups. Patients in the hydrotherapy group who said they would have otherwise been at work ($n = 2$) made alternative arrangements in their absence when attending the physiotherapy appointment (such as time off with pay). Patients in the land-therapy group who said they would have otherwise been at work ($n = 4$) made alternative arrangements in their absence (hours rearrangement $n = 1$; time off without loss of pay $n = 2$; time off with loss of pay $n = 1$). However, this difference was not significant (Table 8.10, p.260 and Table 8.11, p.260).

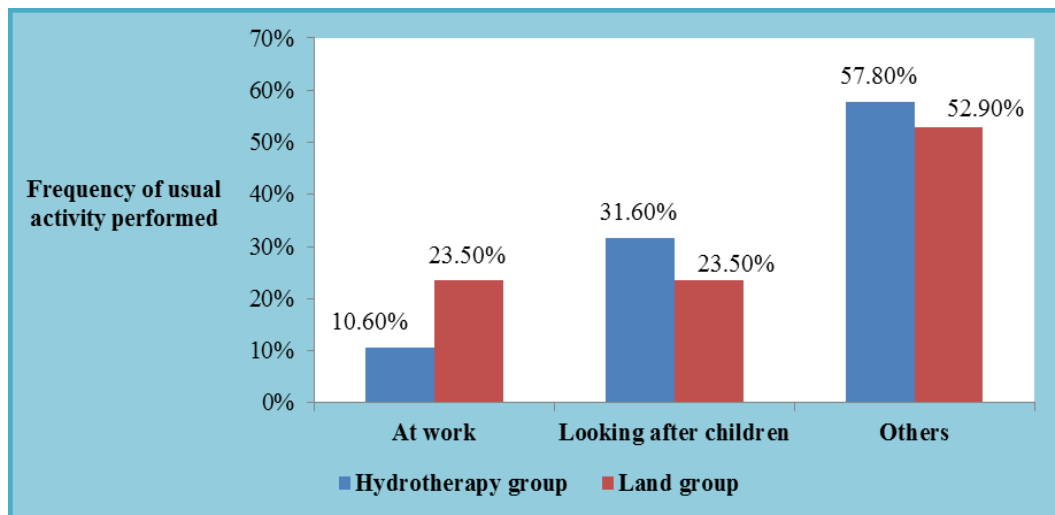


Figure 8.3: Usual activities, performed had patients not had to visit the hospital, between two groups.

While six patients (31.6%) attending hydrotherapy and four patients (23.5%) attending physiotherapy on land reported looking after a child, none reported incurring childcare costs. Six participants in each group were accompanied to physiotherapy. However, the companion in both groups did not have an appointment at hospital, was not in paid occupation and would not have been looking after a child had they not been accompanying the patient, thus no childcare costs were incurred.

Table 8.9: Summary of time travel and wait at hospital, and total time lost during one visit to physiotherapy. The number of treatments received in both groups was multiplied by the total cost of time (time with loss of pay).

	Hydrotherapy group (n = 19)	land-therapy group (n = 17)	p value (95% CI)
	Mean \pm SD (Range)	Mean \pm SD (Range)	
Time lost travelling (min)	64 \pm 44 (20 to 200)	48 \pm 23 (20 to 90)	0.366 (-37 to 14)
Time lost at hospital (min)	58 \pm 28 (30 to 120)	61 \pm 34 (30 to 150)	0.712 (-17 to 25)
Total time lost (min)	120 \pm 57 (50 to 250)	110 \pm 45 (50 to 190)	0.555 (-46 to 25)
Cost (£) of time lost during all visits	0 \pm 0 (0 to 0)	17 \pm 30 (4 to 133)	N/A
Key: SD: Standard deviation NA: Not applicable Min: minutes			

For either group, whether a patient should have been doing ‘other’ activities, or childcare, there were no significant differences in the cost of their time (Tables 8.10, p.262 and 8.11, p.262).

Table 8.10: Time lost during hospital attendance and its total cost for those who would have otherwise been looking after a child whilst attending hospital in both groups.

	Hydrotherapy group (n= 19)	Land-therapy group (n= 17)	p value (95% CI)
	Mean \pm SD (Range)	Mean \pm SD (Range)	
n = (%)	6 (31.6)	4 (23.5)	
Time lost from travel (min)	76.6 \pm 28.7 (40 to 120)	60 \pm 21.6 (40 to 90)	0.397 (-20 to 45)
Time lost at hospital (min)	57.5 \pm 22 (30 to 90)	52.5 \pm 9.6 (40 to 60)	0.745 (-49 to 36)
Total time lost (min)	129 \pm 43 (75 to 180)	112 \pm 28.7 (90 to 150)	0.806 (-51 to 64)
Cost (£) of time lost during all visits	38.5 \pm 19 (13 to 503)	16.7 \pm 15.7 (7 to 40)	0.097 (-39 to 26)
Key: SD: Standard deviation Min: minutes			

Table 8.11: Time lost during hospital attendance and its total cost for those who would have undertaking 'other' activities whilst attending hospital in both group.

	Hydrotherapy group (n= 19)	Land-therapy group (n= 17)	p value (95% CI)
	Mean \pm SD (Range)	Mean \pm SD (Range)	
n= (%)	11 (57.8)	9 (52.9)	
Time lost from travel (min)	59 \pm 51 (20 to 200)	43 \pm 16 (20 to 60)	0.100 (-64 to 5.4)
Time lost at hospital (min)	68.6 \pm 41.8 (30 to 150)	43 \pm 9 (30 to 60)	0.774 (-26 to 35)
Total time lost (min)	127.7 \pm 65.5 (50 to 250)	86.6 \pm 21.6 (60 to 120)	0.301 (-75 to 24)
Cost (£) of time lost during all visits	41 \pm 36 (3.72 to 111)	35 \pm 33 (6 to 108)	0.690 (-39 to 26)
Key: SD: Standard deviation Min: minutes			

8.7.1.3 Societal cost

Hydrotherapy and land therapy showed similar costs to society (Table 8.12). Both groups lost similar amounts of time and attended a similar number of sessions. The value of time was similar in both groups. In the hydrotherapy group, the average total cost to society was £60 per patient compared to £64 in the land-therapy group ($p = 0.790$).

Table 8.12: The total cost to society per patient, including time lost in physiotherapy attendance and time spent at hospital, multiplied by number of sessions and value of time (time without loss of pay).

Total cost to society per patient (£) Mean \pm SD (Range)			
	Hydrotherapy group (n = 19)	Land-therapy group (n = 16)	p value (95% CI)
Value of time (£/hour)	5 \pm 1 (4 to 8)	6 \pm 2 (4 to 9)	0.214 (-2 to 8)
Time lost (hour)	2 \pm 1 (1 to 4)	2 \pm 1 (1 to 3)	0.554 (-0.75 to 0.41)
Average number of sessions	6 \pm 0 (6 to 6)	6 \pm 1 (2 to 6)	0.168 (-1 to 0.19)
Total	60 \pm 43 (13 to 198)	64 \pm 48 (12 to 179)	0.790 (-27 to 35)
Key: SD: Standard deviation			

8.7.1.4 Cost utility and cost effectiveness

The change in QALYs over six weeks of intervention (between Test 1 and Test 2) was not significantly different ($p = 0.88$) (Table 8.13, p.262).

Table 8.13: Cost-utility (tariff) analysis of EQ-5D tariff between hydrotherapy and land-therapy groups.

Variables	Hydrotherapy group (n = 19) Mean ± SD (Range)	Land group (n = 17) Mean ± SD (Range)	p value (95% CI)
EQ-5D tariff at baseline	0.62 ± 0.3 (-0.02 to 1)	0.51 ± 0.3 (-0.2 to 1)	0.579 (-0.1 to 0.2)
EQ-5D tariff at 6 weeks	0.61 ± 0.2 (0.1 to 1)	0.51 ± 0.3 (-0.4 to 1)	0.450 (-0.1 to 0.3)
QALY change	-0.01 ± 0.3 (-0.5 to 0.7)	0 ± 0.4 (-1 to 0.8)	0.88 (-0.2 to 0.2)
QALY: 1= Perfect health Key: QALY: Quality Adjustive life year SD: Standard deviation EQ-5D tariff score (0.594 to 1), with 1 being perfect health, and 0.594 being worse than death			

In Study One, the primary outcome measure was the HAQ-DI. The change score was used to measure the effect between groups. Based on the HAQ-DI, the ICER (Figure 8.4, p.263) was calculated. Every one unit of improvement on the HAQ-DI scale using hydrotherapy would cost an additional £197. This was calculated by dividing total NHS cost of one patient treated in hydrotherapy minus total NHS cost of one patient treated on land (Table 8.6, p.253) over change score of HAQ-DI in the hydrotherapy group between Tests 1 and 2 (0.7), minus change score of HAQ-DI in the land-therapy group between Tests 1 and 2 (0.2) (Kobelt, 1996).

$$\text{ICER} = \frac{\text{NHS costs hydrotherapy} - \text{NHS costs land}}{\text{HAQ-DI change effects hydro} - \text{HAQ-DI change effects land}}$$

$$\text{ICER} = \frac{325 - 148}{0.7 - (-0.2)}$$

$$\text{ICER} = \frac{177}{0.9}$$

$$\text{ICER} = \text{£197 per increase in HAQ-DI score}$$

Figure 8.4: Incremental cost effectiveness ratio (ICER) of treatment on a 1:1 basis.

8.8 Numbers needed to treat (NNT)

The NNT in Study Three was 2.5 (Table 8.14); the cost of producing an overall improvement in the HAQ-DI in one patient over six weeks (NNT x the total NHS cost) was £197.

Table 8.14: Number needed to treat (NNT).

	N of patients	N of events ⁵	Risk differences	Number needed to treat (NNT)
Hydrotherapy	21	16	16/21-8/22 = 0.4 (40%)	1/0.4 (= 100/40) = 2.5
Land therapy	22	8		

8.9 Limitations of the cost chapter

From a cost point of view, it would have been interesting if the data had been collected at three or six months after the intervention, as well as at six weeks. Although it is important to understand the immediate impact hydrotherapy has during treatment, for a long-term disease such as RA, long-term costs are equally as essential. An understanding of long-term costs would have provided a greater

⁵ Overall improvement in the HAQ-DI score

insight into the affect hydrotherapy had on the NHS in terms of GP and consultant costs; it would have also given an insight into societal costs in terms of the benefits of returning to work or being able to undertake usual activities, as well as the direct and indirect savings made that were related to the patient.

In Study One, the sample size was based, a priori, on the HAQ-DI. Sample size calculations are generally based on clinical rather than cost data because economic trials run alongside clinical trials. Conventionally, cost data is more variable than clinical data, making it difficult to identify statistical differences at the same level of inferential error (Drummond et al., 2005). To overcome this, the options are to either accept lower levels of precision, for example increase the accepted level of significance ($p > 0.05$), or extend the data collection beyond the point at which the clinical question had been answered. However, to treat and test patients beyond the point at which the clinical question had been answered would be unethical. Issues around determining what size of difference would be economically important and choosing the relevant resource quantity are the major drivers for therapy costs (Drummond et al., 2005).

The aim here was to calculate the cost per QALY using the EQ-5D. This would provide cost-utility results that could be compared across conditions. However, the QALY did not detect any improvements over the six-weeks intervention period. Studies have found problems using the EQ-5D with RA patients. Hurst et al. (1997) has previously described the reliability of the EQ-5D index and EQ-5D VAS as good or better than that of other instruments, including the HAD (Zigmond & Snaith, 1983), ACR (Felson et al., 1993), ESR and VAS-pain except the HAQ-

DI. Some patients with a severe, long-standing case of the disease reported health states of less than 0, i.e. 'worse than death'. Alava et al. (2013) demonstrated that better estimates of the benefits of RA treatments in terms of QALYs will be gained if the HAQ-DI and pain are simultaneously considered instead of the EQ-5D (Alava et al., 2013). This is a new technique and not one that was adopted in this study. Harrison et al. (2010) recommended the inclusion of preference-based scores (e.g. EQ-5D) alongside disease specific measures (e.g. HAQ), as in Study One, because predicting one from the other is unreliable. In an attempt to predict EQ-5D and SF-6D scores from the HAQ, they found that predicted utility scores overestimated baseline values but underestimated change. Predicting utility values from the HAQ will therefore likely underestimate the QALYs of interventions, particularly for patients with active disease. Using the HAQ-DI instead of the EQ-5D facilitated the calculation of ICER and NNT, but it permits disease-specific comparisons only.

This study is the start point for economic evaluations in adult hydrotherapy. A paucity of other studies for comparison means that there is little context upon which to base the findings. Clinicians and managers wishing to use the positive results from this study to inform their own services will require a notion of their own willingness to pay and budget (resources available to them), rather than whether it is good value compared to other physiotherapy interventions.

8.10 Summary

This chapter set out to determine the cost of providing RA patients with hydrotherapy compared to land-based physiotherapy from NHS, patient and societal perspectives.

On a 1:1 basis, the NHS will spend, on average, £177 more per patient on hydrotherapy treatment than on land-therapy treatment. However, when treating patients on a 4:1 basis, that is, four patients at a time in hydrotherapy compared to a single patient on land, hydrotherapy is a more cost-effective treatment and the NHS can save, on average, £65 per patient. For the patient and society, there is no difference in cost whether treated in the hydrotherapy pool or on land.

Because no improvements were found in either group using the EQ-5D, the incremental cost per QALY was not calculated. The ICER was calculated using the HAQ-DI. Providing six sessions of hydrotherapy to four patients is more effective and less costly than providing treatment to one patient on land when measured using the HAQ-DI and so therefore should be adopted.

The overall findings from this chapter have revealed that the provision of hydrotherapy on a class basis for patients with RA is cheaper and more effective to the NHS than treating one patient on land. However, this provision did reduced neither the cost of GP or consultant time, nor that of prescribed medication or to the patient or society.

The following chapter will discuss the findings of the three studies.

CHAPTER NINE: DISCUSSION

9.1 Introduction

The null hypothesis (H_0) for Study One stated: ‘There will be no significant difference in HAQ-DI score between hydrotherapy and land-therapy arms in patients with RA.’ This has been rejected by the evidence from this research study, which has demonstrated that hydrotherapy is an effective treatment for RA in functional improvement. However, there are many factors that have a direct bearing on this statement, all of which have to be considered in their own right. Each factor will be compared and discussed in light of this finding.

Because of the different nature of the three studies, this discussion will be based on the findings from the three interrelated studies and their interpretations: Study One, which evaluated the difference in outcomes and explains the reasons for the difference between those receiving hydrotherapy and those subject to land therapy, Study Two examined the demographic characteristics of the participants and discussed them in relation to other comparator studies, and Study Three, in which the cost of treatments was evaluated. Therefore, the discussions will be presented under three separate headings for ease of reading. Conclusions drawn from this discussion chapter will include the main findings of the three studies and provide areas for future research.

9.2 Study One (RCT)

9.2.1 Introduction

This RCT evaluated the efficacy of hydrotherapy compared to that of land-based exercise for RA patients. The results of the evaluation of physical function (functional ability, pain, and GWB), disease activity, HRQoL and mood symptoms in patients with RA have been presented in Chapter 6. The RCT Study One findings demonstrated that a six-week, once-weekly exercise programme for people with RA treated in the hydrotherapy pool resulted in improvement in functional ability score, reduction in pain score, improvement in GWB, QoL and psychological wellbeing, with no corresponding improvement in the land treatment.

9.2.2 Comparisons of primary outcome measure

HAQ-DI

The HAQ-DI is limited to areas of functional status concerned with the performance of daily tasks (Van den Ende et al., 1997). The positive finding of HAQ-DI change score between both groups ($p < 0.001$) reflects this certainty.

In Study One, improving the functional ability of participants may be at least partially attributable to the warm-water environment of the hydrotherapy pool. Warm water may encourage muscle relaxation and improves muscle strength, endurance, suppleness and aerobic fitness, thus reducing guarding around joints and enhancing movement (Hinman et al., 2007). The physical properties of water such as buoyancy, thermodynamics and viscosity might provide suitable media to maintain joint mobility and strength. Although it is possible that some benefits of

hydrotherapy will be attributable to warm water immersion alone, Hall et al. (1996) confirmed this in a previous RCT in RA, demonstrating superior effects of hydrotherapy over seated immersion alone. Perhaps this indicates that the most important property of the hydrotherapy is the buoyancy of the water, rather than its warmth.

Buoyancy reduces the physical load on the joints and promotes muscle relaxation, thus allowing more pain-free movement and enabling exercise against water resistance. This improves functional ability and stimulates more active exercise of the muscles and joints than would otherwise be possible (Eversden et al., 2007; Hall et al., 1996; Prins, 2009; Schrepfer, 2002). As the warmth of the water has a sedative effect on nerve endings, it therefore reduces pain and discomfort that occurs when nerve endings are stimulated, further to this, joints have more freedom of movement as a result of reduced pain (Bender et al., 2005; Kjellgren et al., 2001).

The positive finding in this study that hydrotherapy improves functional ability is encouraging. However, it is in contrast from the two previous hydrotherapy studies, which have both shown negative findings, namely Sanford Smith et al. (1998) ($p > 0.05$) and Eversden et al. (2007) ($p > 0.09$). However, Bilberg et al. (2005) showed that hydrotherapy significantly improves the overall score of the HAQ-DI in the six months following treatment ($p < 0.05$); however, their study did not show any immediate improvements following treatment. Bilberg et al., (2005) did not use a comparator group in the follow-up period. The small sample

size in the study by Sanford Smith et al. (1998) (n = 24) may be another factor that can account for the negative results of HAQ post treatment.

In Study One, the significant post-treatment improvement in HAQ-DI and its categories (dressing and grooming, walking, hygiene, reach and activities) may be due to the responsiveness of HAQ-DI to the hydrotherapy and its physical properties. Therefore, this may explain, in part, the reason for the trend of improvement in functional ability directly after hydrotherapy sessions. Buoyancy offers the patient joint unloading with relative weightlessness, which enabled performance of active motion with increased ease (Schrepfer, 2002). It seems possible that these results are due to physical properties of water, which enhanced functional activity through improved ROM, strength and decreased pain. This means that for participants in this study, the performance of daily tasks were improved by hydrotherapy.

In the follow-up period at three and six months, the reasons for non-significant findings of HAQ-DI are not clear, but may have something to do with number of participants involved, as 14 out of 21 and 10 out of 21 participants in the hydrotherapy groups completed the programme, respectively, compared to 14 out of 22 and nine out of 22 in the land-therapy group, respectively (Figure 6.1, p.169). Additionally, since this difference has not been found elsewhere in follow-up periods, it is probably due to the physical properties of water having no long-term benefits to improve functional ability. Other explanations of failure to improve functional ability at the follow-up periods might be either that the

participants would have adversely affected their self-efficacy expectations, or that they were not aware of their physical limits (Michael et al., 1995).

Studies have reported limitations in using HAQ-DI for measuring functional ability. Pincus et al. (1983) noted that the degree of patient dissatisfaction from using HAQ-DI might be associated with the amount of perceived difficulty with a task (Pincus et al., 1983), their study demonstrated that the stated capacity of patients might improve or decline significantly within the responses ['with some difficulty' or 'with much difficulty'] because these responses do not give enough boundaries. An alternative is that the patients were sometimes not able to describe their physical limitations because they found it difficult to interpret the question or translate the limitations to fit the answers available.

De Jong et al. (2003) evaluated the effects of long-term land exercise in 309 RA patients. They used HAQ-DI to measure functional ability. However, they found no significant differences in HAQ-DI after two years ($p = 0.09$). They justified these results by claiming that changes in physical impairments and physical function may be weakly associated with changes in the HAQ score. A major weakness of the study is, however, that they have included patients with relatively mild functional impairment in patients with RA; this might explain the HAQ's lack of sensitivity to change.

Conversely, Van den Ende et al. (1997) used the HAQ to determine changes in 100 RA patients following a short-term land exercise programme (12 weeks, three times weekly). The findings suggested that the HAQ was not useful as a

functional outcome measure in short-term exercise trials. However, this study analysed data of patients who were only mildly disabled as measured by HAQ, and this may therefore explain the lack of significant results.

Study One results differed from De Jong et al. (2003) and Van den Ende et al. (1997) in two respects. Firstly, at Test 1, HAQ-DI scores had moderate to severe difficulty or disability showing an overall score of HAQ-DI (1.1 to 2) (Bruce & Fries, 2003). Secondly, the physical properties of water in six sessions per six weeks, as recommended by HyDAT team (2009), provided favourable results. Thus, the findings indicate that HAQ-DI is a worthwhile instrument for use in a hydrotherapy exercise study, at least in the short term. Our participants also showed a marked decrease in pain and increase in function ability.

An implication of this is the possibility that functional ability assessment by HAQ-DI should be considered when assessing patients with RA, and that they may benefit from therapeutic intervention of hydrotherapy directed towards improving their function.

9.2.3 Comparisons of secondary outcome measures

9.2.3.1 Pain (HAQ_{VAS}) and general wellbeing (HAQ-GWB)

HAQ_{VAS}

VAS was used in this study to measure pain, which is part of the two short pages of HAQ. Originally considered to assess arthritis-related pain (presence or absence), VAS was used for pain assessment, measuring the severity of pain in the past week (Bruce & Fries, 2003). This instrument has frequently been used to

evaluate the efficacy of exercises on patients with RA. Pain is one of the most common rheumatological complaints that is assessed in RA patients (Huskisson, 1974).

Huskisson (1974) was the first to report pain intensity in patients with RA by using VAS. In Study One, the participants were asked about pain experienced in the previous week before entering the study, and initial mean VAS scores for pain were recorded as being higher than those reported in previous studies such as Eversden et al. (2007) and Rintala et al. (1996).

The reduction in pain found in the hydrotherapy group is a very significant benefit for such patients. In this sample of patients with RA disease, HAQ_{VAS} was sensitive to change following the six-week programme. These findings further support the idea of pain being relieved after hydrotherapy (Ahern et al., 1995).

A number of different factors may explain reduction in pain post-hydrotherapy. The improvement might be due to the physiological effects of hydrotherapy that induce release of opioid peptides such as Alpha-endorphin, or methionine enkephalin (Bender et al., 2005; Coruzzi et al., 1988). Hydrotherapy has the capability to induce methionine enkephalin plasma levels, associated with a fall in blood pressure and heart rate (Coruzzi et al., 1988). Endorphins and enkephalins are suggested to play a leading role in endogenous anti-nociception because endogenous opioid peptides are released from immune cells and have strong immune-modulatory effects (Lesniak & Lipkowski, 2011).

There are, however, other possible explanations for reduction of pain that might be related to a pain-gate theory. The gate-control theory of pain by Melzack & Wall (1965), suggests that the transmission of nerve impulses from afferent fibres to spinal cord transmission (T) cells is modulated by a spinal gating mechanism in the dorsal horn (Melzack, 1993). A mechanism in the dorsal horns of the spinal cord acts like a gate that inhibits nociceptors' transmission from the body to the spinal cord and then to the brain through polysynaptic interneurons (Melzack & Wall, 1965; Melzack, 1993).

The spinal gating mechanism is influenced also by nerve impulses that descend from the brain. The observed decrease in pain could be attributed to the pain gate theory that pain is relieved through exercises in warm water that enhance the blood flow and facilitate the closure of the 'gate' in the spinal cord (Melzack, 1993). This is why hydrotherapy is used as a pain-relieving treatment and patients experience an immediate effect with short-term carry over, but does not last over time. Further studies are required to determine the pathway in which hydrotherapy reduces pain in patients with RA.

There is an important theory in personality psychology, the 'locus of control' (Phares, 1976; Spector, 1988). Psychological factors like locus of control play a role in adaptation to chronic illness such as RA (Phares, 1976; Spector, 1988). The main question addressed in this section is whether improvement in pain and other psychological-wellbeing terms, such as depression and wellbeing, might be attributed to locus of control, and whether this might be another possible explanation for relieved pain.

Locus-of-control theory was developed in 1954 by Julian Rotter, who discussed how the degree of control individuals believe they over events will affect their behaviour (Rotter, 1954; Rotter, 1966). There are two type of locus of control – internal and external (Rotter, 1954; Rotter, 1966). Internal control is when the person believes they can control the events that happen in their life (Rotter, 1954; Rotter, 1966). Conversely, external locus of control means that their decisions and life events are controlled by environmental factors, which they cannot influence (Cross et al., 2006).

It has been proposed that patients with chronic pain and external locus of control do not believe in recovery, and thus avoid increasing their activity level, and report poor ability to reduce and control their pain, compared to those with internal locus of control, who may develop strategies to deal with pain and thus report lower pain-intensity (Crisson & Keefe, 1988; Cross et al., 2006; Gustafsson & Gaston-Johansson, 1996). This means that their response to the intervention may depend on which locus of control is dominant.

For instance, if patients with high internal locus of control believe that they have improved post-hydrotherapy, they might attribute this to their performance in the pool and reflect this response when completing the questionnaires. On the other hand, if patients with high internal locus of control felt that they had not improved post-treatment, they might attribute this to their tiredness or lack of focus on their performance in the pool.

When it comes to participants with high external locus of control who believe they had improved after the pool treatment, they might attribute this to the expertise of the therapist who had treated them, while those who felt they had not improved might attribute this to the lack of expertise of the physiotherapists. This type of behaviour might play a role when the participants filled out the questionnaires. Similarly, this type of behaviour in personality psychology might also have an impact on health behaviour, as those with an internal locus of control are likely to feel in control of their own health and feel capable of performing the necessary behaviours to preserve health (Cross et al., 2006).

In the follow-up period (3 months) in Study One, no significant changes were found in either of the two groups. A possible explanation for some of our results may lie with other factors relating to the disease itself, which might have contributed to the lessening of pain; however, there is no definitive factor that this can be explained by.

In the literature, VAS was used in three studies: Eversden et al. (2007), Rintala et al. (1996) and Stenström et al. (1991). Study One's findings are consistent with those of Rintala et al. (1996) ($p \leq 0.05$), which used VAS pain as a primary outcome measure, while both studies found that there was a statistically significant reduction in the pain level of RA patients after hydrotherapy. However, Eversden et al. (2007) ($p = 0.40$) and Stenström et al. (1991) ($p > 0.05$) found no significant improvement in the pain level following their interventions. Hall et al. (1996) found that all patients demonstrated a significant pain reduction ($p \leq 0.005$) when using the McGill pain Questionnaire (scale, 0-100) (Melzack, 1975).

Therefore, our patients' response was in accordance with other findings in the literature.

The major finding in Study One was the fact that pain experienced by the hydrotherapy group decreased significantly during the six-week treatment period. The implication of this study's findings is that pain intensity should be measured when assessing RA patients, and that they may therefore benefit from therapeutic intervention directed towards alleviating their pain in the short-term. However, the long-term efficacy of hydrotherapy is inconclusive. Furthermore, knowing pain intensity in these patients will help clinicians to evaluate the effectiveness of pain management in RA.

HAQ-GWB

HAQ-GWB measures the global health status of the patients' GWB. In the Study One, HAQ-GWB was shown to have significant positive findings among RA hydrotherapy participants compared to the land-therapy group. The significant finding of global wellbeing indicates that RA patients, when treated using hydrotherapy, experienced better global health status compared to those in the land-based exercise group. Unfortunately, however, no available data were found in the literature relating to HAQ-GWB for comparison with these findings.

All the previous studies only used HAQ-DI to measure functional ability rather than physical function. It has already been stated that GWB could be called psychological wellbeing (Bowling, 2004) because it could be used to measure self-reporting of intrapersonal affective or emotional states reflecting a sense of

subjective wellbeing or distress (Badia et al., 1996; Dupuy, 1984). The reason for improved GWB post-hydrotherapy is not clear, but it may have something to do with locus of control due to the fact that pain was improved, and this still reflects a general improvement in wellbeing.

The present researcher is unaware of any study that has reported the effectiveness of any of these treatment methods for GWB management in patients with RA. Therefore, future studies may be directed towards developing a strategy for improving GWB in patients with RA.

The implication of this finding is that GWB should be considered when assessing RA patients, and that they might benefit from therapeutic intervention. The reported improvement in wellbeing among these patients should give practitioners ideas for promoting and increasing wellbeing.

9.2.3.2 Health related quality of life (HRQOL or QoL)

HRQoL was measured by EQ-5D – that is, a two-part instrument, EQ-5D tariff (with its descriptive profile) and EQ-5D_{VAS}.

EQ-5D_{VAS}

The second part of HRQoL, called EQ-5D_{VAS}, records the subject's self-assessed VAS, rating health on a vertical line on which the best- and worst-imaginable health states score 100 and 0, respectively. One of the most interesting findings in Study One was that the self-rated global health status measured by the EQ-5D_{VAS} showed significant findings between the group comparison post-treatment ($p = 0.002$), change score between Test 1 and Test 2 ($p = 0.021$), and within the

hydrotherapy group between Test1 and Test 2 ($p < 0.001$). This result may be explained by the fact that hydrotherapy improved pain, functional ability, psychological wellbeing and consequently, improved general-health status. The findings in this study further support the claim of Hurst et al. (1997) who state that the EQ-5D_{VAS} is reliable and clearly useful for measuring changes in perceived health. These results suggest that the EQ-5D_{VAS} is a helpful self-valuation tool for patients with chronic diseases such as RA.

The non-significant findings in the score of EQ-5D_{VAS} over time (follow-up period of three and six months, or change-score difference between Test 1 and 3 or Test 2 and 3) might be explained when patients appraise their own health using this scale (EQ-5D_{VAS}), however it cannot be expected that RA patients will assess their health in the same way over time because their perceptions of the disease severity will alter.

Another explanation might be due to other factors influencing their disease course, such as exacerbation of disease activity and pain, as it is impossible to predict the trajectory of a systemic inflammatory disease such as RA. The EQ-5D_{VAS} is recommended to clinicians who wish to use it as a quick and easy tool to measure a patient's overall health and recovery.

EQ-5D tariff and EQ-5D profile

In this study, a time trade off (TTO) procedure was used to elicit utility weights for EQ-5D tariff health state because since the start of this study, a set of values has been obtained from a large sample (3,395) of the adult population of England,

Scotland and Wales (Dolan et al., 1995; Kind et al., 1998). This weighting presents on a scale on which full health and death score one and zero, respectively.

In this study, the descriptive profile of EQ-5D was summarised demonstrating the frequency or the proportion of reported problems in each level for each dimension. Two studies investigated the validity\reliability and responsiveness of EQ-5D tariff in patients with RA (Eversden et al., 2007; Hurst et al., 1997). The present research findings on EQ-5D tariff are discussed in relation to these two studies.

Study One produced no changes in the mean score of EQ-5D tariff in either group of RA patients at Test 1, Test 2, Test 3 or Test 4. No change was noted in the change score either. This could be due to a lack of sensitivity of the EQ-5D (Rabin et al., 2011a) when observing patients with mild to moderate RA. A lack of sensitivity was one reason as to why the EQ-5D 5L was developed. The EQ-5D 5L increases the number of alternative health states to 3,127 from 245 in the 3L (Rabin et al., 2011b).

The reason for the lack of effect measured using the EQ-5D tariff is not clear; one possible explanation might be the patient's denial of adjustment to chronic disease, and it has been previously stated that health-state assessments differ according to experience of illness (Hurst et al., 1997). In the reviewed hydrotherapy literature, Eversden et al. (2007) was the only study that used QoL tools in terms of EQ-5D tariff and EQ-5D _{VAS}, but no significant finding was

found in either HRQoL. The finding was similar even in a larger study by Eversden et al. (2007). However, the findings of Study One do not support the research study by Hurst et al. (1997), which stated that the EQ-5D tariff was highly responsive to self-reported improvement.

There is no generally accepted definition or method to measure HRQoL, as the boundaries between health and disease are poorly defined; consequently, measurement of health is problematic (Carr et al., 1996; Hurst et al., 1997). The essential requirement of any instrument claiming to measure health outcomes is the ability to detect clinically important changes (Hurst et al., 1997). Analysing EQ-5D profile dimensions individually allowed this study to identify which activities presented problems for RA patients, this was possible because the RA sample in the study was small (43 patients).

Firstly, it was shown that more than two thirds of patients reported problems in all dimensions at Test 1, Test 2 and Test 3. Secondly, as expected, elderly people reported more problems in all dimensions. Thirdly, no improvements were noted in all dimensions between groups except for the pain and discomfort dimension in the hydrotherapy group alone, and the number of patients who reported problems at Test 1 (n = 17/21) declined in Test 2 (n = 14/21) and in Test 3 (n = 4/14) (Figure 6.2 and 6.3 in page 182).

It was not expected that improvement in pain and discomfort would continue during the follow-up period, but this was a very positive finding. It was not possible for this study to determine the reason for this improvement where

responses were given using agreement scales. One major drawback of analysing individual dimensions is that it reduces the external validity by reducing the numbers available for comparison between each group.

Study One has been unable to explain why the anxiety/depression dimension of EQ-5D profile did not show any improvement over time, especially in the hydrotherapy group, as the outcome measures of psychological wellbeing showed significant improvement in change score when measured by the HADs, HAD-D and HAD-A. The reason for this is not clear but it may reflect the responses of the patients who did not completely understand the direct questions within EQ-5D profile when they filled in the questionnaires. It may also reflect its lack of depth and sensitivity for this domain. The EQ-5D profile may be indicated as a simple health profile, clarifying the areas in which a patient or group of patients is recording problems, and the areas in which changes have arisen over time.

The contradictory results of both EQ-5D profile and EQ-5D_{VAS} may be explained by the fact that the two instruments are measuring different aspects of health status or HRQoL. The tariff for EQ-5D is derived from using TTO methodology as the EQ-5D tariff is commonly used to evaluate cost utility studies and resource allocation (Drummond et al., 2005) compared to direct scoring of self-valuation health status. However, both EQ-5D profile and EQ-5D_{VAS} showed good results in this study and it can be determined that these instruments are highly responsive to self-reported improvement in RA, and that this reveals clinically important changes.

It is hoped that the results of Study One will help clinicians improve the level of QoL in RA patients by providing appropriate treatment. Such treatment may include medical and/or psychological support and counselling, all of which should benefit the patient (Strand & Singh, 2010).

9.2.3.3 Disease-activity parameters

DAS28

This thesis did not find any significant difference in the disease activity indices measured by DAS28 score between hydrotherapy and land exercise group. In the hydrotherapy group, DAS28 improved from 4.28 in Test 1 to 2.49 in Test 2 compared to the land-therapy group, where it improved from 4.31 in Test 1 to 3.28 in Test 2. Despite these data not reaching a statistically significant difference ($p = 0.613$), this score change has a trend to remission of the disease, as DAS28 < 2.6 corresponds with being in remission according to the ACR criteria (Fransen et al., 2003).

There was no previous literature that had used this tool to measure disease activity in hydrotherapy. Sanford Smith et al. (1998), Stenström et al. (1991) and Hall et al. (1996) all used the Ritchie Articular Index (RAI) to assess disease activity (Ritchie et al., 1968). However, their results, showed no significant difference. In contrast, Hall et al. (1996) found significant reduction in joint tenderness in their hydrotherapy group post-treatment. These inconsistent results may be explained by the fact that a number of different factors affect disease activity parameters. In the DAS28, for example, when all other markers of inflammation and RA disease activity are in remission, the patient remains with many tender joints and therefore

the score may be misleadingly high. Alternatively, if the patient never had a very high ESR blood result (even during a flare-up), or if RA affected the feet (feet are not included in the 28-joint count), the score may be misleadingly low.

It can sometimes be challenging to decide whether an individual joint is swollen or tender, even when assessed by the same person on different occasions or when assessed by several people on a single occasion and this uncertainty may lead to misleading inconsistencies in the scores. Even with supervision (which occurred in this study), the participants found it difficult to make decisions about the swelling of a joint. Measurement of DAS28 is routinely employed in rheumatology departments, giving the rheumatologist the opportunity to change the treatment accordingly.

The study did not show a statistically significant difference ($p = 0.613$) in disease activity measured by DAS28 after hydrotherapy. Although these results differ from the study carried out by Hall et al. (1996), which found a significant reduction in joint tenderness in a number of joints in the hydrotherapy group ($p = 0.03$), but they are consistent with some other published studies that measured other disease activity indices (Bilberg et al., 2005; Sanford Smith et al., 1998; Stenström et al., 1991). The findings of this study suggest that RA as a chronic disease is particularly difficult to assess. This is because the symptoms are extensive in terms of joint pain and stiffness with subsequent loss of function and later deformity, and they often vary spontaneously from day to day.

RADAI

The RADAI is an alternative method to clinician assessment of disease activity. The main aim of the RADAI is to offer an easy to use assessment in disease activity where laboratory measurements or clinical assessments may not be possible or are too demanding (Fransen, 2003; Mason et al., 1992; Stucki et al., 1995). In this study, the overall score of RADAI was not improved clinically or statistically in either group and remained unchanged in the hydrotherapy group (4.5 in Test 1 to 4 in Test 2) and (3.9 in Test 1 and 4.5 in Test 2) in the land-therapy group.

This result may be explained by the fact that RA is an inflammatory systemic disease, and disease activity features such as tenderness, swelling and blood markers reflect directly whether the course of disease is in exacerbation or in remission. Thus, these disease activity indices might not be affected directly or easily by hydrotherapy or land therapy. Other possible explanations for these results may be that the participants cannot rate swelling accurately as was remarked on earlier, or it might be difficult for patients to discriminate between RA signs and symptoms such as pain, swelling and stiffness. Another possible explanation for the negative results is that the small sample size in Study One – mainly in the follow-up period – could perhaps explain the non-significant finding for the RADAI.

The major goal of RADAI score in RA patients' management and in RA clinical studies is to evaluate disease activity over time. Further large sample studies will be needed in the future to find out if RADAI is sufficient to guide clinicians in RA

management strategy compared to the DAS28. Both DAS28 and RADAI aim to measure the same underlying construct, namely arthritis inflammatory activity, but from different content and perspectives (Fransen et al., 2003); i.e. DAS28 depends on physician judgment, whereas RADAI depends on patient's perception of the complaint (Fransen, 2003). However, there may be some reasons (practical and economic) to replace the assessment performed by the physicians (DAS28) with a patients' questionnaire (RADAI). The fact that both disease activity indices perform similarly well does not mean that one can be automatically replaced with the other (Fransen, 2003). Both RADAI and DAS28 have different content and because the non-significant difference that were observed in Study One for both of them, it seems other factors might influence its findings.

Three studies have tried to evaluate grip strength following hydrotherapy such as Hall et al. (1996), Sanford Smith et al. (1998) and Bilberg et al. (2005). However, their findings were contradictory. In Study One, the grip strength was not measured for the following reasons:

- It is never measured in clinical practice as a disease activity index in SRFT;
- The equipment to measure it was not available in (i) clinics, (ii) the gym, (iii) physio outpatient or (iv) hydrotherapy;
- Inter-rater reliability concerns (because this is not routinely measured at SRFT).

Another essential feature of RA is fatigue, which is a frequently occurring symptom in RA patients. Unfortunately, in this study fatigue was not investigated for the following reasons:

- Causes and mechanisms that lead to fatigue in RA and other autoimmune diseases are conflicting, with several variables acting at different amounts in different patients at different times, either singly or in combination (Hewlett et al., 2011; Hewlett et al., 2008) (See page 30).
- Fatigue need to be investigated and derived more likely by using cross-sectional study rather than longitudinal study to find out the cause at certain time (Hewlett et al., 2011).

9.2.3.4 Psychological wellbeing (mood symptoms) (HADs)

HADs

HADs were developed as a screening tool to identify probable cases of anxiety and depression among individuals in hospital clinics with non-psychiatric conditions (Bjelland et al., 2002). The hydrotherapy group showed significant improvement between Test 1 and Test 2 for HADs and its subdivisions (HAD-D and HAD-A) compared to the land group, but this improvement was not maintained in the follow-up period. In the hydrotherapy literature, only one study done by Hall et al. (1996), investigated the psychological functioning of RA patients. Hall et al. (1996) measured the psychological wellbeing of mood and tension by using AIMS-2 (Meenan et al., 1992), and found greater improvements in hydrotherapy during the follow-up period only.

The researcher believes that it is unfair to compare the results reported by Hall et al. (1996) with those observed in Study One for three reasons:

- The study design was completely different; Hall et al. (1996) used four groups with randomisation concealment allocation, compared to the two groups in Study One.
- The duration and frequency of aquatic exercise intervention was variable in the study by Hall et al. (1996).
- Hall et al. (1996) examined mood and tension as part of a functional ability questionnaire called (AIMS-2), while HADs was used in Study One as a separate questionnaire to measure depression and anxiety.

In Study One, improvement in anxiety and depression in the hydrotherapy group might be related to the fact that the improvement on functional ability skills and pain relief reflects directly on the improvement in mood changes among RA hydrotherapy participants. Moreover, increased production of opioid peptides such as methionine-enkephalin post-hydrotherapy has a strong anticonvulsant, antidepressant and antianxiety effect (Coruzzi et al., 1988; Lesniak & Lipkowski, 2011).

Other possible explanations as to improvement in aspects of patients' psychological wellbeing, such as anxiety and depression, may be due to Rotter's psychological theory of personality related to the locus of control.

In the RA population, the prevalence of depression and anxiety have been reported to range from 13 to 20% (Covic et al., 2012; Dickens et al., 2002) and from 21 to 70%, respectively (Uguz et al., 2009; Covic et al., 2012). In Study One, the prevalence of depression was 35% – which is far higher than the general RA population – and the prevalence of anxiety was 30%. However, the study sample representing the general RA population (n = 169) (Covic et al., 2012), was substantially larger than the current study sample in Study One (n = 43).

Both studies have used self-report measures, and the prevalence of depressive symptoms was about 40%. Even if the symptoms of depression and/or anxiety may be subclinical, they have a major impact on physical function (Covic et al., 2009). The results of increased prevalence of depression may be due to disease chronicity or clinical fluctuation of disease between exacerbation and remission in RA. All these factors may contribute to psychological morbidity in patients with RA. It is important to consider the psychological effects of RA, as this relates not only to physical functions, but also to many social interaction, which has a direct effect on wellbeing.

9.2.4 Correlations discussion

Correlation between RADAI & DAS28

Both land and all combined RA patients show significant positive moderate correlation compared to no correlation in the hydrotherapy group. Stucki et al. (1995) found moderate correlation between RADAI and CRP ($r = 0.54$, $p < 0.010$) and RADAI and swelling-joint count ($r = 0.43$, $p < 0.01$) in RA patients. However, the findings of Study One do not support the findings of previous

research studies, which report no or relatively low correlation of other types of patient questionnaires, such as EQ-5D_{VAS} and AIMS2, with laboratory parameters of disease activity such as CRP or ESR (Hurst et al., 1997; Riemsma et al., 1996). Literature study showed that the DAS28 and RADAI are realistically moderately related ($r = 0.53$) (Fransen, 2003), however, this does not automatically mean that one can be replaced by the other.

To our knowledge, no hydrotherapy literature used RADAI, DAS28, or even association between them. The result of Study One showed that the rating of patient perception for pain, swelling, tenderness and MS in RA patients was essential in order to assess the problem of disease activity in some circumstances. This is necessary to achieve valid patient perceptions. Moreover, compatibility of patient perception with physician's judgement will enhance the reliability of interpretations about the underlying disease process for patient management.

Furthermore, the different content and focus of RADAI and DAS28 could explain the contradictory results between them in the hydrotherapy group. The main advantage of the DAS28 is that it compared 28 joint counts rather than 44 joints, however, blood samples still had to be analysed which is time consuming and sometimes costly. Self-assessment of RA disease activity by the patient may save work for the physician (Fransen et al., 2003) but its reliability is open to question. RADAI as a self-administered questionnaire of disease activity is related to, but does not automatically replace, other indices of disease activity, such as the DAS28.

The relationships between depression scores (HAD-D) and educational levels, RF, disease duration, morning stiffness, DAS28 and RDAI

The aim of this section was to determine any association between depression or anxiety with low education level, DD, MS, RF and disease activity indices. In this study, the prevalence of depression in the hydrotherapy group was 47% and 23% in the land-therapy group, and it is approximately 35% in all patients, which is relatively higher than that reported in the literature (Covic et al., 2012). Initially it was intended to include anti-CCP in the analysis of the data, but there was a lack of available data because two-thirds of cases did not report this test in their medical notes. Therefore, this research study was unable to include anti-CCP in the analysis. Only RDAI in Test 2 shows a positive significant correlation with depression score.

Prior studies have noted the association of depression and anxiety with low education levels, longer DD and poor clinical outcome in RA cases (Evers et al., 2002; Isik et al., 2007). However, Isik et al. (2007) justified the reasons as to why the prevalence of depression highly correlated with low ELs in their Turkish study, these reasons being low socioeconomic status, insufficient social support and a chronic disabling disease (Isik et al., 2007).

In Study One, the reasons for finding no correlation are not clear, however it might be due to the small sample size in the study. There was a significant correlation between depression score and RDAI score in all patients post-treatment ($p < 0.001$, $r = 0.578$). This finding is consistent with those of Katz and Yelin (1993). On the other hand, no correlation was found between the depression

score and DAS28 post-treatment. This discrepancy of correlation between depression score and DAS28, and depression score and RADAI score, may be because of using a self-report questionnaire such as HADs to measure depressive symptoms, and the self-report questionnaire such as RADAI to measure disease activity, because as discussed earlier, DAS28 content differs from RADAI.

In reviewing the literature, no data were found on the association between depression or anxiety and MS. As MS is part of disease activity indices and RADAI categories, the non-association between them is not clear.

It has been argued in the literature about the association of RF levels with cases of psychiatric disorders. In Study One, no correlation was found between depression score and RF. Although the thesis findings were different to some published studies (Ahokas, 1986; Isik et al., 2007; Legros et al., 1985), they are consistent with others (DeLisi et al., 1984; Sane et al., 1990). For instance, in Study One, RF was positive in about 60% of the RA cases, however, there was no significant correlation with depression score ($p = 0.782$). It has been recommended that a high depression score may be of greater importance to RA patients with positive RF rather than other measurable variables (Isik et al., 2007). This was not supported in Study One.

These findings may help us to understand how many factors have an association with a higher score of depression in chronic diseases such as RA. Therefore, future studies to examine this correlation should be carried out with a larger sample of patients with RA (Isik et al., 2007).

The relationships between anxiety scores (HAD-A) and educational levels, RF, disease duration, morning stiffness, DAS28 and RADA

The prevalence of anxiety in hydrotherapy, land therapy and all patients were 38%, 23% and 30% respectively. All these percentages are within the range of anxiety prevalence in the general RA population. Again, no correlations were found between anxiety score and EL, MS, DD, RF and DAS28.

A moderate positive correlation was found between the anxiety score and RADA in the land-therapy group and in all patients. Although anxiety and depression are not the same, they do often present the same symptoms and therefore the explanations for anxiety might be similar to the depression score in the former section. Isik et al. (2007) found that DD was less correlated in anxiety scores than depression. They found moderate positive correlation between the degree of depression and DD ($r = 0.341$, $p = 0.05$,) and strong negative correlation between the DD and degree of anxiety ($r = -0.642$, $p = 0.05$).

A previous study by VanDyke et al. (2004) reported that in RA cases, the clinical feature of anxiety occurred earlier than depression, and it preceded the clinical finding of depression. This idea is supported by Isik et al. (2007) who emphasised that when DD is prolonged, the anxiety score declined and depression score increased. However, in this study this is not the case, as no correlations were found between DD and anxiety. Hawley & Wolfe (1988) stated that the level of anxiety is the same whether the condition is inflammatory such as RA, or non-inflammatory such as OA, FMS and backache.

A number of studies have reported the association of psychiatric disorders with the immune system (Herbert & Cohen, 1993; Irwin, 2002). However, it was not possible in this study to establish a firm association between the immune system parameters (RF and anti-CCP) and psychiatric disorders. Because more than two-thirds of the participants in Study One did not have confirmation of anti-CCP antibodies included in their medical notes, the researcher was unable to include this important immunological parameter in the correlation section. This test is done at diagnosis, and as the notes available for the study were only from 2003, if the doctors had not transferred this data to the more recent post-2003 electronic notes, then they were not available for analysis in this study. However, NICE guidelines (2009) stated that in patients with suspected RA, testing of anti-CCP should be considered only if RF is negative and/or in decision-making combination therapy. An implication of this is the possibility to determine factors responsible or those, which correlate with high score of anxiety or depression in RA.

9.2.5 Predictive factors for functional disability (HAQ-DI)

The results of this section yielded important findings about the potential relation of predictors of the functional disability as measured by HAQ-DI. Functional disability in RA patients was predicted by poor QoL, high depression and anxiety scores, poor GWB and by a high score of RADA. Further analysis, using the multivariate regression analysis suggests that of these variables, the only significant predictor was poor GWB.

Predictors of functional disability were analysed previously by several longitudinal retrospective and prospective studies. These studies have examined the possible link of predictors between different parameters, such as radiological and biological factors in the development of disability in patients with RA (Toussirot, 2010). However, either the results of such studies – which aimed to determine prognostic factors – are heterogeneous because of variations in the length of the observation period, or the choice of criteria used to measure physical disability was at fault (Toussirot, 2010; Wolfe et al., 2003; Leigh & Fries, 1992). In addition, there were inconsistencies and variations in baseline parameters, treatments modalities, patient selection criteria and DD (Toussirot, 2010).

In Study One, five independent variables were found as potential predictors of functional disability. This reflects the multidimensional nature of functional disability in RA. The HAQ score provides an insight into the overall consequences of the RA disease in terms of disease severity and the impact it has on psychological wellbeing and QoL (Toussirot, 2010).

In Study One, psychological wellbeing such as depression and anxiety were predictors of functional impairment in patients with RA. The relationships between elevated depression/anxiety scores with functional disability signify that RA patients may have difficulties in managing household chores in their daily activities. However, it is unclear from this present cross-sectional study whether functional disability is a cause of poor psychological wellbeing or vice versa, and it therefore requires a longitudinal study to determine the direction of causality.

The impact of anxiety and depression in RA patients' lives is most likely to be enormous. The positive association between increased depressive symptoms with high HAQ DI scores in RA patients show that they may have difficulties in social interaction and caring for themselves at home. This finding is consistent with previous studies such as Wolfe & Hawley (1993) and Abdel-Nasser et al. (1998), who found that patients with high depressive symptoms are most likely to experience intense pain as measured by VAS pain and physical disability (Wolfe & Hawley, 1993).

Additionally, it has been reported that a high anxiety score was related to increased physical disability in patients with RA (Wolfe & Hawley, 1998; VanDyke et al., 2004). Others have commented that anxious RA patients are less likely to cope with their normal work-related activities because of pain and increased physical disability, which may lead to early retirement and dependency on families and carers (Lillegraven & Kvien, 2007; De Croon et al., 2004). Ødegård et al. (2005) identified that poor psychological-health status, such as helplessness, was a predictor of inability to work in RA patients.

Disease activity measured by RADAI was one of the predictive factors of physical disability in RA patients. It reflects that intense/high disease activity has a detrimental effect in coping with daily activities. Therefore, RA patients have to be regularly monitored and encouraged to be involved in a mild general exercise programme such as daily walking to reduce the impact of the disease.

It is interesting that in this study DAS28 (which assesses the degree of disease severity in RA patients) was not a predictor of functional disability in RA patients. Therefore, caution is required in the interpretation of this finding because of the small sample size of the study. The researcher is not aware of any previous study using RADA1 as a predictor in patients with RA.

Few studies have reported other disease activity indices such as pain, MS and decrease in grip strength, which were all predictors of disability (Wolfe & Cathey, 1991). Moreover, Leigh & Fries (1992) found tender-joint count was a predictor of poor outcome in RA patients. Van Zeben et al. (1993) found that the number of swollen joints and Ritchie index were predictive of increased physical disability using HAQ-DI (Van Zeben et al., 1993). Van Leeuwen and colleagues (1994) followed 149 patients with early RA for three years and showed that a high functional disability score appeared to be determined and predicted by joint tenderness with no clear relationship to joint swelling.

Additionally, Study One, GWB and HRQoL measured by EQ-5D tariff were found to be the best predictors of functional disability in RA patients. This finding is consistent with Leigh & Fries (1992), who also confirmed that overall health status was found to be a predictor for functional outcome in RA patients (Leigh & Fries, 1992). There are no other studies that examined EQ-5D tariff and its predictive ability of HAQ-DI. Therefore, replication of this study's findings in other settings with larger sample sizes is worthy of consideration.

To sum up, a variety of independent variables were revealed in this section as predictors for functional disability at baseline in all RA patients. The findings of this section show that higher score of depression, anxiety, RADA1 and GWB and low score of EQ-5D tariff were predictors of functional disability in RA patients. Therefore, patients presenting with numerous recognised predictive factors for ‘poor outcome’, including physical disability, should be closely monitored and provided with appropriate educational support and psychological intervention (Toussiro1, 2010).

9.2.6 Discussion of the exercise protocol between hydrotherapy and land-therapy in RA patients

The mean number of sessions attended by participants in both groups were the same (six sessions each). This demonstrated that all RA participants had equal participation in the treatment protocol. It has been suggested by many authors/researchers that failure to adhere to an exercise programme is a common problem in RA patients (Roddy et al., 2005; Campbell et al., 2001). One of the mandatory factors for improving physical function, QoL and GWB is the patient’s adherence (Belza et al., 2002).

However, the adherence rate in Study One seems to be acceptable for the following reasons:

- RCT occurred within NHS services with easy access for all participants;
- It was carried out under the supervision of highly qualified health professions and in a supportive environment;

- It was offered as part of a full MDT package of care in a large rheumatology department within SRFT, which may have encouraged participants to attend the full programme.

A daily diary was provided to all patients by the physiotherapist, but not as part of the study, as a reminder to perform the exercise programme every day, especially as the patients knew that the therapist would be reviewing the diary at the next session as part of follow-up (Heine et al., 2012). This diary might be used as an opening discussion about the success or difficulties in the performance of the exercise programme since the last appointment, and could be used in deciding progression or regression of the exercise programme. In Study One, the numbers of sessions are carried out in accordance with a recent survey in the UK HyDAT Team (2009). However, there is no consensus about frequency or duration of hydrotherapy sessions in any literature study.

All participants in both groups performed similar exercise programmes in terms of aims, short- and long-term goals, HEPs, general rehabilitation, mobility and functional treatment, and education and advice. The only exception was instructions around on how to manage flare-ups (Appendix 25).

General fitness level, pain and joint symptoms are an important concern in patients with RA in order to reduce flare-ups. Thus, the main goal of any therapeutic intervention should be to reduce this clinical component of the disease. Although an average of six treatments was received by both groups, it is unclear whether the improvements in the hydrotherapy group resulted from

exercise or from other factors, such medical therapy, the degree of participant attention or motivation, or the care provided by the healthcare professionals. It is possible that most of the improvement seen was attributable to the interventions used, as RA is an autoimmune disease and would be expected to cause a progressive exacerbation or even remission of the participants' conditions.

All efforts were made to reduce the amount of the researcher's bias due to treatment. The gatekeeper physiotherapist responsible for instruction in the exercise programme was aware of the purpose of the study and tried to be impartial with both groups. Hydrotherapy staff were different from land-therapy staff and the therapists were not involved with testing. However, bias might be a factor because they were not blind.

9.3 Study Two (Kellgren study)

9.3.1 Descriptive comparison of mean age, gender, disease duration and social support

This study demonstrated that the mean age for referral to hydrotherapy was 60 years. Findings from Arthritis Research UK (2011) and NICE (2009) supported this. When comparing the finding of mean age with other hydrotherapy studies, there was little difference between Eversden et al. (2007) and Hall et al. (1996), who both concurred with the findings of this study, whereas a relatively slight difference with HyDAT Team (2009) and Bilberg et al. (2005) was shown. The HyDAT team emphasised that the optimal age of patients referred to the hydrotherapy treatment among UK patients with chronic disease was 51 years (HyDAT Team, 2009).

The knowledge gained through this research shows that there is no certain evidence suggesting a standard age and DD of RA patients. The NICE guidelines (2009) identified that the peak age of incidence of RA in the UK for both genders is in the 70s, which is supported by Arthritis Research UK (2011). This researcher maintains that although there is no evidence giving the exact mean age that RA patients are referred for hydrotherapy. However, the researcher believes that referral of patients to hydrotherapy might happen any time after diagnosis. The referral depends on many factors such as patient's need, treatment goal, and physicians' satisfaction. This comparison between the participants in Study One, the general RA population in the Kellgren Centre and general RA population in the UK implies that our sample does reflect the RA population, and that there are no differences that might affect or influence the findings in mean age and DD. In spite of that, patients with any long-term DD should have the facility to access hydrotherapy (HyDAT Team, 2009).

Most studies have emphasised that the incidence of RA is higher in women than in men (Arthritis Research UK, 2011). This finding was confirmed in Study Two, which showed that more than 70% of current participants who were referred to either group were female. The female/male ratio varied between 2:1 (Arthritis Research UK, 2011), 3:1 (Temprano & Smith, 2011), 4:2 (NICE, 2009) and 2.5:1 (Tehirian & Bathon, 2008). The differences in the ratio of women to men can be explained in part by an influence of reproductive and hormonal factors such as oestrogen and progesterone in females, which could potentially explain some of

the gender effects, thus predisposing females to RA; this has been discussed in research performed by Silman & Pearson (2002).

Between the comparator studies, the percentage of females was relatively smaller approximately between 62% and 89% in all reviewed studies. Bilbeg et al. (2005) included forty-two females and five males, and the small size of his sample means it is difficult to make his findings generalisable. This may therefore explain in part the reason for the limitations of his study, which did not allow for gender bias. It remains unclear as to what the precise explanation is for the greater prevalence of RA in females and what the physiological role of hormones is in this gender divide (Silman & Pearson, 2002). Although their studies did offer evidence of the predisposition of female hormones towards RA, their conclusions were not satisfactorily proven.

There is very little discussion about DD in epidemiological studies. In this study, participants had lived for 10 years with RA, but the DD and expected survival of RA patients might be related to the disease severity and the age when the patient developed RA. The most important point is that the DD between the patients of the Kellgren Centre and those in Study One was the same, reflecting the same features of the general RA population that had been referred to hydrotherapy (as found in Chapter 7, p.210). This is clinically important as both groups have the same survival period with relatively different conditions. It presents a factor, which increases this study's generalisability, again a significant point for future research. Within this study, the disablement of the participants bears witness to the downhill trajectory of the motor facility of those with RA.

No certain data or exact figures were obtained regarding socio-economic items, such as occupation or marital status that influenced the prognosis and the course of the disease, rather than the risk of developing RA (Albers et al., 1999). There is general agreement throughout research studies that this disease does have a very significant impact on individuals' work ability and family income, as well as on society (Arthritis Research UK, 2011). These data demonstrate that there are many different factors that may influence the risk of developing RA. Providing this information to patients and society is essential in providing the knowledge about the trajectory of the disease and the ability to assess the needs of the health service in the future.

However, in Study Two most participants referred to the exercise programmes were generally between employments or retired rather than unemployed or work-disabled. Approximately one third of people had stopped working within two years of onset because of the disease, and this prevalence increases thereafter (NICE, 2009; Verstappen et al., 2004).

9.3.2 Descriptive comparison of obesity and body mass index (BMI)

The study carried out in the Kellgren Centre and in the hydrotherapy pool found that the number of obese patients was consistent with that of other studies in the UK, such as Zaninotto et al. (2006). They suggest that more than 35% of patients were overweight and 25% were obese. Several studies have addressed the effects of obesity on CVD risk in RA, and show that obesity does present extra risk (Stavropoulos-Kalinoglou et al., 2011). Very few studies have reported the role of obesity in RA patients, as evidence from the general population leads to a very

clear assumption that obesity might influence RA patients' health status and outcome (Stavropoulos-Kalinoglou et al., 2011).

A worldwide study done by Naranjo et al. (2008) included 4,363 patients from 48 sites in 15 countries, and found that more than 18% of RA patients were obese. Conversely, a UK-based study by Armstrong et al. (2006) found that 31% of RA patients were obese. Both studies reported that more than 55% of RA patients were overweight or obese. It is interesting to note that in RA, the prevalence of overweight and obese sufferers seems to be subject to geographical variation (WHO Consultation, 2000).

In Study Two, the exact cause of increased prevalence of obesity and overweightness in RA patients remains unknown. However, there are many possible contributors that might influence BMI in RA patients (Stavropoulos-Kalinoglou et al. 2009). Increased bodyweight might be associated with low level of physical activity and an inactive lifestyle. Inflammation, even though this is suggested to affect body composition, might be a reason for an increase or decrease in BMI.

An underweight state might be associated with other factor such as a low energy intake. Therefore, increasing physical activity is important for obesity control and improving energy, and thus nutritional intake may prevent an underweight state. To the knowledge of the present researcher, there are no widely accepted validated strategies to control obesity in RA. Overall, obesity is a very poorly studied subject in RA. Its causes and the potential interventions to prevent or

reverse it have received even less scientific attention (Stavropoulos-Kalinoglou et al., 2009). To conclude, patients who were referred to hydrotherapy or a land-based programme for rehabilitation were similar in BMI scores in comparison to general RA patients.

9.3.3 Descriptive comparison of smoking and hypertension (HT)

Over the past century, there has been a dramatic increase in the use of tobacco (Alamanos & Drosos, 2005). Cigarette smoking has been suggested to influence both the risk and course of RA and other autoimmune diseases (Alamanos & Drosos, 2005; Papadopoulos et al., 2005; Hardy et al., 1998). Several epidemiological studies (cross-sectional or longitudinal studies) have investigated the relationship between smoking, severity and outcome of the disease and increased risk of RA (Wilson & Goldsmith, 1999; Saag et al., 2008; Harrison, 2002; Symmons et al., 1997). This association was very clear in patients who were heavy smokers and in those with seropositive RF. At present, the mechanism by which smoking could influence RA activity and severity is vague (Papadopoulos et al., 2005). Harrison, (2002) points out this mechanism may be due to the direct effect of smoking on the disease process by inducing the production of RF or by activating the immune system (Harrison, 2002). However, the percentages of active smokers in both the Kellgren and the RCT study were clearly very low (6% and 12% respectively) in comparison with the general health population in England and other comparator studies such as Hutchinson et al. (2001) (42%), Manfredsdottir et al. (2006) (34%) and The Information Centre for Health and Social Care in England (2011) (20%). This might be explained by the

emphasis of education programmes in recent years on explaining the dangers of smoking in RA, or it might be because of the change in smoking laws.

It is interesting to note that in all previous RA studies related to HT there is a very wide range of HT prevalence between studies. It ranges from 3.8% to 78% (Panoulas et al., 2008). It is difficult to explain why HT studies show such wide prevalence, but it could be related to the different populations assessed, the diverse sample sizes and significant differences in the definition of HT used (Panoulas et al., 2008). Some of these studies, for example, such as McEntegart et al. (2001), Solomon et al. (2004) and Wolfe et al. (2003), compared the RA population with general RA population, whereas other studies, such as Chung et al. (2008), Del Rincón et al. (2001), Dessein et al. (2002) and Dessein et al. (2005) compared RA with controls. Moreover, the sample sizes among these studies were variable. Solomon et al. (2004) used a sample of 287 RA patients compared to the 87,019 sample of the general RA population. Conversely, Dessein et al. (2002) used 79 RA patients compared to 39 OA patients. In Study Two, approximately 30% of participants referred to the exercise programme have HT.

Many factors might be directly or indirectly associated with increased prevalence of HT in RA patients. These factors can be classified into disease, lifestyle, and medication. Chronic inflammatory diseases such as RA have been associated with arterial stiffness, which may subsequently lead to increased arterial BP, and might explain the high prevalence of HT in RA (Franklin, 2005). The development of HT in chronic systemic inflammatory diseases such as RA might be caused by many mechanisms, such as an increase level of CRP, vasoconstriction, leucocyte

adherence and platelet activation (Devaraj et al., 2003). NSAIDs, C/S and DMARDs, which are used to treat RA patients, cause fluid retention and might cause an increase in blood pressure. This again is a consideration for future research. Sometimes a lack of adherence to long-term therapy for a usually asymptomatic condition such as HT might be another reason for increased prevalence of HT in RA (Panoulas et al., 2008). Other conditions such as IHD and atherosclerosis, which increase the prevalence of HT, are common in RA, mainly in the elderly age group (Panoulas et al., 2008). Despite this, extrapolations such as these cannot be made to all patients, as direct evidence as to whether the prevalence of HT is greater among patients with RA than in the general population is still inconsistent (Solomon et al., 2003; Han et al., 2006).

9.3.4 Descriptive comparison of rheumatoid factor (RF)

Presence of RF in RA has prognostic significance (Bas et al., 2003; Jansen et al., 2002). It has been recommended that RA patients with seropositive RF have a more aggressive disease, whereas in those with sero-negative RA, the disease is less severe and less deforming (Dörner et al., 2004; Jansen et al., 2002). In Study Two, more than 60% of participants reported positive RF in their medical notes, which reflects the general population of RA. IgG and IgM are present in up to 90% of RA patients (Waldburger & Firestein, 2008; Dörner et al., 2004). However, these autoantibodies are also produced during any chronic infection, malignancy and a variety of autoimmune and inflammatory syndromes (Waller, 1940; Temprano & Smith, 2011). Moreover, 1-4% of healthy individuals and more than 25% of elderly people have RF detectable in their serum in low titre (Waldburger & Firestein, 2008).

The presence of RF does not confirm RA, because, as stated by Arthritis Research UK (2011), one out of 20 people have positive RF but do not have RA, and eight out of 10 patients with RA have positive RF. The results of this investigation show that some people with RA never develop RF, and at the onset of the condition, only approximately half of people with RA have positive RF (Arthritis Research UK, 2011). Accordingly, negative RF does not confirm the absence of RA (Arthritis Research UK, 2011). When checking the past results of our patients it was possible to see that not all of them were shown to have positive RF on diagnosis (Table 6.3, p. 173).

One of the research questions that could be asked in future planning include whether the result findings will differ between RF positive or negative in RA patients with larger sample sizes.

9.3.5 Descriptive comparison of disease activity measured by DAS28

Clinical, laboratory and radiographic measures are important components in the assessment of RA patients, and play a key role in the evaluation, treatment and prognosis of disease course (Waldburger & Firestein, 2008). DAS28 is one of the main common formulas used in clinical practice. It incorporates both clinical and laboratory variables such as tender-joint count, swollen-joint count, patient self-assessment of disease activity VAS and ESR (Prevoo et al., 1995; Aletaha & Smolen, 2005). DAS28 is increasingly being used as an endpoint in clinical trials and is widely indicated for use in clinical practice for monitoring and guiding disease activity and treatment decisions (Prevoo et al., 1995; Waldburger &

Firestein, 2008). In clinical practice, the overall assessment of disease activity depends on the number of tender and swollen joints, which are regarded as dominant variables (Waldburger & Firestein, 2008).

It has been suggested in the literature that hydrotherapy might decrease joint tenderness and increase range of movement. This may be because the hydrostatic pressure of water immersion leads to reduced oedema (Campion, 1997; Hall et al., 1996). In the Kellgren Study Two, only 171/200 patients had reported the DAS28 score in their medical notes compared to all 43 of the patients in Study One. However, the trend for DAS28 in both groups was similar. The key problem with this explanation is that DAS28 reflects directly the inflammatory process of RA, and this might not be influenced directly by hydrotherapy or land therapy.

9.3.6 Descriptive comparison of medication and comorbidities

Treatment of RA included several classes of drugs such as NSAIDs, DMARDs, C/S and biologic drug modifier (Temprano & Smith, 2011). This study has found that, generally, biologic drugs were reported in both Study One and Study Two compared to the reviewed hydrotherapy studies, which did not report any biologic medication (Figure 7.15, p.217). This might be explained by the fact that biologic drugs were introduced recently, after comparison studies were carried out. It might also be because they require specific criteria for indication and were excluded from previous studies.

All studies in Figure 7.15 (p.217) reported variable medication, being either combination or single-drug therapy. The highest percentage of drug treatment

commonly reported and used by patients was DMARDs and NSAIDs. All studies reported using combination therapy. Combination therapy appears to be helpful for RA patients whose disease outcomes fail to respond to monotherapy with DMARDs (O'Dell et al., 1996). As a result, it is difficult to exclude patients from a trial because they are using medication. Medication may always exist, therefore, as an uncertain confounder.

It is recommended that DMARDs are the most important treatment modality in the successful management of RA, mainly when they are introduced early (Singh et al., 2012; Temprano & Smith, 2011). The research studies reported combination therapy rather than mono-therapy in their participants' medical notes. This was also the case in our participants' notes. Recently, it has been suggested that the most common combination therapy, lately updated from 2008 to 2012 by the ACR criteria, to be between DMARDs and biologics drugs. In the 2012 statement, it now includes more than eight types of biologics drugs, while the 2008 statement included only five types (Singh et al., 2012). The more modern combination therapy should offer an avenue for more research. In the literature studies reviewed and presented in Figure 7.15 (p.217), only a few percent reported using C/S. This might be explained by the controversy regarding of the use of this medication (Myasoedova et al., 2011).

It has been implied that there may be a complex relationship between RA and comorbid conditions (Michaud & Wolfe, 2007). Thus, it is important to recognise and account for such illnesses in the holistic care of the patient, as well as in understanding research outcomes. Because RA has numerous outcomes,

including, among others, functional ability, hospitalisation, work disability, QoL and increased medical costs, a different pattern of comorbid illness is evident in Figure 7.16 (p.217) (Michaud & Wolfe, 2007). Diverse comorbid conditions influence such outcomes differently.

Diverse comorbid conditions with RA, such as Diabetes Mellitus, thyroid problems, respiratory disease and cardiac disease, have been reported in the RCT Study One and the Kellgren Study Two. Consequently, these comorbid conditions make them significant for RA outcomes research because they interfere with important RA outcomes.

9.4 Study Three

9.4.1 Introduction

Study Three is the first to evaluate the cost of hydrotherapy in RA. Previously, only six studies have examined the effectiveness of hydrotherapy in an RA population. There are no published studies of the costs or cost-effectiveness of hydrotherapy in the RA population. Chapter 8 was designed in order to evaluate the cost of hydrotherapy and land-based therapy in an RA population from an NHS, patient and societal perspective.

Previous studies have reported the economic efficacy of hydrotherapy on other rheumatic diseases such as OA, FMS and JIA (Cochrane et al., 2005; Epps et al., 2005; Gusi & Tomas-Carus, 2008; Patrick et al., 2001). Unfortunately, there are no studies available for appraisal to help resolve some of the contradictory findings. The major finding of this study was that hydrotherapy was more

effective and less costly in treating four patients in the pool compared to one patient on land.

9.4.2 NHS Costs

Using hydrotherapy to treat RA patients on a 1:1 basis is intuitively more costly than treatment on land. The greatest contributor to this extra average cost of £177 per patient was the physiotherapy staffing costs. In this study, as per hospital protocol, staffing for the hydrotherapy group included a physiotherapist and assistant. Assistance may be required to help patients enter and exit the pool and in case of emergencies. This is for several reasons, namely that 25% of patients have a pathology or dysfunction described as severe; 20% of patients have some communication or sensory difficulties; 74% of patients have some mobility, or co-existing mobility difficulties; and 27% of patients have associated risk factors such as heart conditions or epilepsy (HyDAT Team, 2009). Therefore, from a staffing viewpoint, hydrotherapy will, on average, be two times more costly than land treatment.

In Study Three, physiotherapist and assistant costs were calculated using the median full-time equivalent of Band 5 and 3, respectively. Seventeen per cent of clinicians involved in the treatment of hydrotherapy patients are Band 5 or equivalent, 48.5% are Band 6 or 7, and 12% are at specialist or consultant level (HyDAT Team, 2009). The researcher found that it was the same physiotherapist treating the patients on land and in hydrotherapy. The researcher therefore realised that staffing costs could be increased or decreased accordingly, but that it is

probable that the same level of staffing costs should be applied to land therapy and hydrotherapy.

Hydrotherapy pools come in different shapes and sizes according to monetary resources and the space available prior to the installation. Size will dictate the ability to treat patients individually or in groups. Treating more than one patient at a time will reduce costs, assuming that the staffing level for those extra patients does not also increase. Previous studies have used group hydrotherapy, including Patrick et al. (2001), whose group sizes ranged from six to 40; Eversden et al. (2007), which used groups of one to four; Bilberg et al. (2005) which used groups of eight to nine; and Stenström et al. (1991), which used groups of five. The HyDAT Team (2009) reported that 31% of hydrotherapy occurs in groups, although there was no information about the size of the group, the ratio of staff to patients, the size of pool, or the type of pathology most commonly treated in groups (HyDAT Team, 2009).

Clinically, patients with RA are offered one-to-one treatment on land rather than group work due to concerns about their risk of flare up and the non-uniformity of their presentation. In the Study Three, a sensitivity analysis on the number of patients treated in hydrotherapy and on land was carried out. The cost of treating one extra person in hydrotherapy was £83 based on four subjects in a group, compared to £37 on land. Although this can be calculated in cost terms, it is not certain that the effect of the treatment in a group on land would be the same as in the current study. However, treating four patients in the pool was much cheaper (£83) than treating one patient on the land (£148). It should also be acknowledged

that land-based group therapy is becoming more common, partly because hydrotherapy pools are closing, and further research is required to determine whether land-based group therapy can produce similar benefits to individual therapy. This would have important implications for delivery cost.

The second contributor to the discrepancy in NHS costs was equipment, although this discrepancy was not as large as first imagined. It is important to emphasise that in this study the cost of installing a pool was not included. Firstly, the cost of pool installation at the hospitals studied was not available, and secondly, costs would vary depending on the size, age and position of the pool in the hospital. It was the intention of this study to determine the incremental cost of treatment, including equipment, not capital outlay of pool. Hospitals that already have pools can use the results of Study Three to calculate ongoing costs. Those that do not have pools can use the results plus the capital outlay of a new pool.

The advice for clinicians and managers is that if there is already a hydrotherapy pool that permits group therapy, better outcomes may be observed from hydrotherapy compared to those on land. If resource allocators are planning a hydrotherapy service for RA patients, a pool large enough to accommodate a minimum of four patients should be considered.

There were no observed differences regarding the number of physiotherapy sessions attended between groups. Due to the ongoing nature of the disease, hydrotherapy was restricted to six sessions; all participants in this trial received an average of six sessions of treatment. Although this number differs from the

frequency of hydrotherapy sessions provided in other studies appraised in the literature (see Chapter Four, p.115), the median number of hydrotherapy sessions in the UK is six (HyDAT Team, 2009).

From an NHS perspective, over the six-week course of treatment, average GP and medication costs between groups were similar, and no consultant costs were incurred. The treatment for both groups meant that consultant appointments were not necessary, and one group did not visit their GP more than the other. This could be explained by the short follow-up period of six weeks. It is possible that costs would have been different if they had been collected over a longer term.

9.4.3 Patient costs

Time, travel and other costs, such as out-of-pocket expenses borne by patients who use NHS services are an important part of an economic evaluation because they are associated with utilisation of health services (Epps et al., 2005; Gusi & Tomas-Carus, 2008; Goodwin & Morrissey, 2003; Drummond et al., 2005).

Travel expenses were similar in each group, as was the distance travelled to and from hospital. One person in the hydrotherapy group required an ambulance to and from hospital and another used a taxi, which increased the average cost, whilst two patients in the land-therapy group lived close enough to walk. Only one person used the tram to get to hospital, a mode of transport peculiar to Salford and Manchester. One person in the land-therapy group was referred to occupational therapy that incurred a cost of £6.40, whilst one patient received six

sessions of acupuncture at the same time as hydrotherapy, incurring a cost of £210.

Around half of the participants in each group were retired and 5% in the hydrotherapy group considered themselves to be a homemaker. The HyDAT Team (2009) also reported that almost half of all hydrotherapy patients did not consider themselves to be employed, and that a third had been retired for more than two years. Time associated with travel and clinical attendance was costed according to forgone activities. The demographics of the patients in this study and their activities are reflected in the small cost of time lost with loss of pay. Overall, the costs patients incurred were not statistically different, whether they attended hydrotherapy or land therapy.

9.4.4 Costs to society

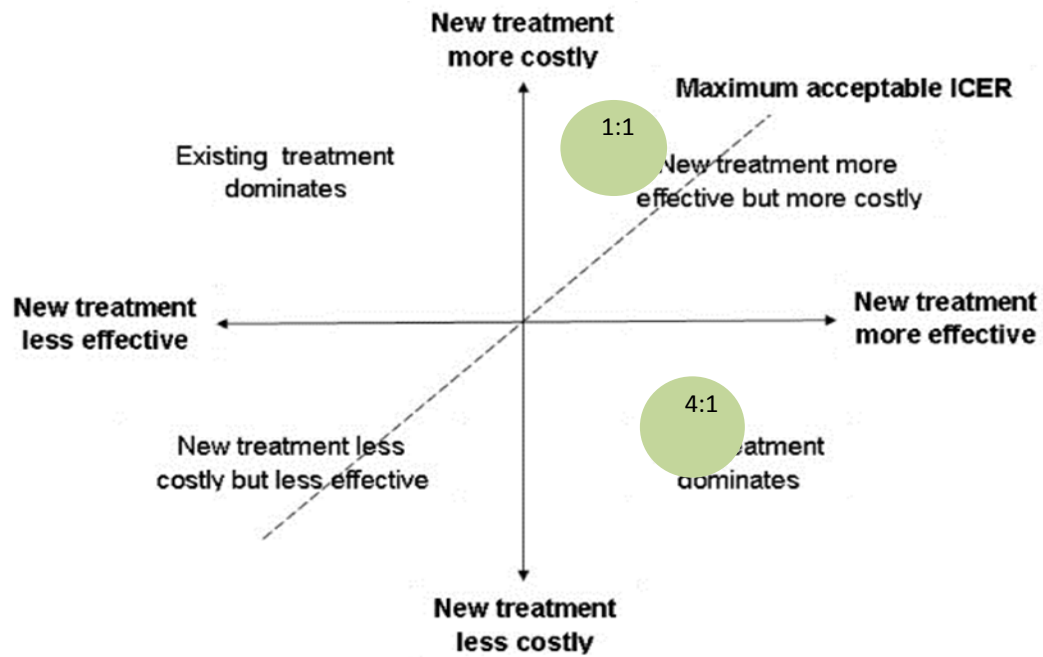
The cost to society was similar whether patients received hydrotherapy or land therapy. There were similarities between the groups in terms of the time lost travelling, time lost at the hospital and total time lost, probably due to the similarity in the groups' demographics. From the societal perspective, for those participants claiming housework or leisure activities, the value of time (AWR) was multiplied by £4.46, and the value of time at employer's cost was calculated at £7.77 for females and £8.7 for men. The value of participants who were employed in the hydrotherapy group (four) and in the land-therapy group (six) was calculated by multiplying the cost by 21.2% to reflect employers' National Insurance and superannuation contributions.

For this thesis study population, approximately half of the RA patients were retired and a minority employed, the cost incurred to society and the patient was similar. Where more of the population are employed, the cost to society would potentially be greater. Although the number of participants in both groups was different, 16 in the land-therapy group versus 19 in hydrotherapy, there were more than twice the number of employed patients in the land-therapy group than those in the hydrotherapy group.

9.4.5 Cost effectiveness

In Study Three, the ICER was calculated using the HAQ-DI. This study demonstrated that with a patient ratio of 4:1, hydrotherapy was more effective and less costly than land therapy and should therefore be implemented. However, where this is not possible and the alternative of 1:1 is used, for every one unit of improvement on the HAQ-DI scale from hydrotherapy, it would cost an additional £197 more than land therapy.

The CE plane can demonstrate where the maximum acceptable ICER lies and where in relation to that the intervention of interest lies. The maximum acceptable ICER is dependent on the resources available and the willingness to pay. Figure 8.5 (p.318) demonstrates that when the ratio of patients treated in the pool to those treated on land is 4:1, hydrotherapy is dominant in terms of cost and effectiveness. Hypothetically, when the ratio is changed to 1:1, it moves into the area where it becomes more effective, but more costly.



● = Hydrotherapy treatment with a patient ratio of either: 4:1 [four in hydrotherapy and one on land] or 1:1 [one in hydrotherapy and one on land].

Figure 8.5: Cost effectiveness plane.

The NNT in Study Three, is the number of people needed to receive hydrotherapy to produce an overall improvement in the HAQ-DI in one patient (McQuay & Moore, 1997). The optimal NNT is one; meaning that every time a treatment is used on the defined patient group, it will result in a desired positive outcome that would not have occurred without treatment (Dalton & Keating, 2000). Therefore, in the current study, a NNT of 2.5 means that 10 patients need to be treated with hydrotherapy before they can be sure of achieving improvements in the HAQ-DI in four patients, that would not be gained by treatment on land. A NNT between two and five is categorised as a successful therapy, and NNT of 20 or more may be useful in prophylaxis (McQuay & Moore, 1997). Knowing that the treatment is successful in terms of the cost and the number of patients that need to be treated

helps calculate how much the expected gains will cost, both in financial terms and in terms of the demands on the patient to continue the therapy (Dalton & Keating, 2000).

Dalton and Keating (2000) described the use of NNT, its use in physiotherapy and its benefits to clinicians. Despite this, it is not widely used in physiotherapy literature. To be useful, other studies of hydrotherapy are needed that, firstly, offer alternatives to this study, and secondly, have calculated the NTT. Comparisons can then be made using the NNT amongst other factors such as cost, age, epidemiology, population needs, social factors and other local priorities (Watt & Burrell, 2001).

9. 5 Overall summary of discussion

The first section of this chapter discussed the merits of hydrotherapy against the land exercise programme when assessing functional ability, disease activity, QoL and psychological wellbeing. Again, the focus in this chapter was discussing the differences and assessing the merits of each programme. There was discussion on the longer-term effects of hydrotherapy and no very clear conclusion was reached; but with a disease that has a high pain-content, any relief of pain, for however long, can be considered to have some success. The protocols for each treatment were similar, but one finding from this study emphasised the need for adherence to the regime by the patients for more positive outcomes.

This second part of this chapter has compared and discussed the main factors in the two groups of RA patients who participated in this study. Comparisons have

been made between the demographic similarities and differences, which were discussed in the literature and were assessed with the findings in this study. Any differences that appeared between the hydrotherapy and the land-therapy group could be attributed to the choice of patient which, although was random, had to be at the discretion of the professionals – namely the physiotherapists and consultants.

The final section of this chapter discussed the financial implications of the two treatments. The findings of this study demonstrated that although hydrotherapy was less costly in treatment and personnel there was very little difference in other variables. The beneficial effects and lower cost of hydrotherapy over land exercises might mean that hydrotherapy is considered the better choice of treatment. This chapter also examined the generalisability of this study. Despite the small number of participants, the rigorousness of the methodology gives veracity to the results, and it could be accepted that these findings do have relevance for other units and will give a sound base for further research.

The following chapter discusses the summary, economic evaluation, strength, weakness, recommendations and implications of this study.

CHAPTER TEN:

SUMMARY, RECOMMENDATIONS AND

CONCLUSIONS

10.1 Introduction

A few studies have investigated the effects of hydrotherapy as a treatment modality for RA patients, but their findings have been inconclusive and unclear. This research team's knowledge of the effects of hydrotherapy in RA patients in terms of healthcare utilisation is limited by the lack of published results. The central research problem evaluated in this work concerned the effects of hydrotherapy compared to the land therapy in RA individuals (Study One) in terms of the physical function, disease activity, psychological wellbeing and QoL.

Few studies have investigated the epidemiological features of RA compared to a sample of RA population within the same area. Therefore, this study compared the characteristics of RA patients from Study One with the patients in the Kellgren rheumatology centre of CMFT and previous rheumatology studies.

Healthcare utilisation was also evaluated in this study (Study Three) to demonstrate whether hydrotherapy is more costly than other interventions, such as land therapy, from the perspectives of the healthcare provider, patients and society. This final chapter presents the summary of the findings, recommendations, strengths, limitations, methodological quality, learning key and conclusions drawn from the present investigations.

10.2 Summary

Aims of the thesis

The primary aim of this thesis was to:

Evaluate the difference in outcomes for RA patients when treated with hydrotherapy as opposed to land-based therapy.

The secondary aims of this thesis were to:

- Determine the effect of hydrotherapy in the management of patients with RA by conducting a systematic review;
- Identify and evaluate the differences in demographic factors between the hydrotherapy and land-therapy groups;
- Identify and understand the reasons for the difference in functional ability measured by HAQ-DI between those receiving hydrotherapy and those receiving land therapy;
- Evaluate whether or not hydrotherapy could improve pain and GWB, HRQoL, disease activity and mood symptoms (depression and anxiety) more effectively than land therapy in patients with RA;
- Determine the association between variables measuring disease activity; determine the association between variables measuring psychological status with socio-demographic features and disease activity indices;
- Determine which factors predict functional disability;
- Describe and compare patient characteristics from Study One with patients from a regional rheumatology centre and previous rheumatology studies;

- To evaluate the cost of hydrotherapy compared to the land-based treatment, from the viewpoint of the provider [NHS], patient and society.

10.2.1 Findings of the study

To fulfil the aims of the research study, the functional ability of patients was measured by HAQ-DI, which showed that the hydrotherapy group benefited more than the land-exercise group in the short term.

The secondary aims of this thesis included many factors. The systematic literature review highlighted and provided the encouraging evidence to suggest that hydrotherapy is an effective intervention for relieving pain, health status compared to an alternative such as land therapy, home exercise and control group.

Study One demonstrated that pain, which is a significant factor in chronic disease, was mitigated by hydrotherapy. The benefits of this pain relief were not sustained after the 6-week follow-up period. These findings demonstrate that there is better functional ability and respite from pain, even if only for short periods for those with RA. Therefore, because of these research findings, the research might offer a well-supported argument for treatment of RA patients by hydrotherapy rather than with land therapy. Additionally, these findings provide suggestions and a base for further research work giving supporting references through this study.

There was a significant improvement in GWB for the hydrotherapy group compared to the land-therapy group in post treatment and follow-up, which led to a better health status for these patients. This must be considered when addressing hydrotherapy provision.

HRQoL measured by EQ-5D_{VAS} showed significant improvement for the hydrotherapy group compared to the land-therapy group. The descriptive profile of EQ-5D dimension for pain and discomfort showed a trend of improvement in the hydrotherapy group (post-treatment and in the follow-up period) compared to the land-therapy group. Again, this would offer opportunities for further research into the importance of pain relief in long-term diseases. Because RA is a chronic disease with strong associations to pain it opens the question of the long-term effects of short-term benefits.

Positive moderate correlation was found between disease activities indices (RADAI and DAS28) in all RA patients and in the land-therapy group. Similarly, moderate correlation of depression scores was found with disease activity measured by RADAI in all RA patients in both the land-therapy and hydrotherapy groups. Additionally, moderate associations were found between anxiety score and RADAI in all RA patients, in both the land-therapy and hydrotherapy groups. Further studies should consider to examine the association between the disease activity and depression.

Predictors of functional disability at baseline in all RA patients were RADAI, EQ-5D tariff, HAQ-GWB, depression score and anxiety score. However, combined univariate regression showed that HAQ-GWB was the only predictor of functional ability.

Study Two provided evidence that the sample in Study One showed similar demographic data in terms of: mean age, DD, gender, BMI, RF, HT, DAS28 initial mean score, medication, comorbidities and occupational status, to that of

literature on a similar topic and a sample of 200 patients from a regional centre for RA in Manchester. Limitations of data reported in the medical notes were considered. Further research could be done into the external validity of RCTs, particularly in relation to the measured treatment effect.

Study Three was the first to examine the costs of providing hydrotherapy compared to those of providing land-therapy from the perspectives of provider, patients and society. The findings have revealed that the provision of hydrotherapy on a group basis for RA patients was cheaper and more effective than that of one-to-one land therapy.

10.3 Strengths and weaknesses of the study

All studies have inherent strengths and limitations; these are highlighted in this section.

The innovations and benefits of this thesis

This thesis is the first that has examined and evaluated the economic costs of hydrotherapy compared to those of land-based therapy in RA patients. It involved 36 RA patients (11 males and 25 females). Therefore, the inclusion of an economic analysis provides strength to the study.

Only one study in the RA hydrotherapy literature investigated psychological wellbeing as part of functional outcome measure called AIMS2 (Hall et al., 1996). This is the first study in RA hydrotherapy literature studies to use HADs to determine the effectiveness of hydrotherapy on ‘psychological wellbeing’. Therefore, further studies are required to examine the efficacy of hydrotherapy in improving psychological wellbeing in the long-term.

The periods of follow-up in Study One were three and six months. It was an attempt to provide further evidence regarding the longer-term effects of hydrotherapy compared to land therapy. The rationales of having follow-up intervals were to ascertain for how long the benefits of hydrotherapy would last. Because it was shown that the benefits of hydrotherapy were not long term, more research is need to discover how to extend these benefits for longer. Inadequate duration of treatment and/or follow-up is another common difficulty for the external validity of RCTs (Rothwell, 2005).

This thesis is the first that has examined a wide range of outcome measures. The assessment methods used in Study One are regarded as comprehensive methods to measure physical function, QoL, disease activity, and psychological wellbeing. Moreover, the outcome measures used in this study are mandatory when used as an expression of clinical implications in disease activity, physical function, psychological wellbeing and QoL; these are all being used in clinical practice.

The external validity of an RCT also depends on whether the outcomes were clinically relevant (Rothwell, 2005). Few studies have considered disease activity such as tenderness, swelling, grip strength and MS. This study has examined disease activity by including the DAS28 and RADAI and the correlation between them. The study instruments used were a self-administered questionnaire and the physicians' assessment of disease activity. The DAS28 is commonly used in rheumatology departments within the NHS.

Correlations of psychological wellbeing, such as the depression score and anxiety score, along with categorical data such as EL, MS, RF and DD were tested in

Study One. There is no literature showing that hydrotherapy studies have examined this before. The wider ranges of correlation given in this study would be helpful in providing a base for further study in the future as part of the assessment and treatment in RA patients.

The sample size in Study One was appropriately powered based on HAQ existing data (Bilberg et al., 2005). This sample size is larger than the studies of Sanford Smith et al. (1998) and Rintala et al. (1996) who studied 24 and 34 RA patients respectively. However, it is possible to question the sample size as the intended sample size was not met, but research has shown that if the methodology is rigorous, the small size of the sample can be negated when looking for generalisation (Slavin & Smith, 2009; Rothwell, 2005). This further provides evidence in support of the originality of the studies in this thesis.

No previous hydrotherapy RA studies have examined the predictors of disability in patients with RA. This is another major advantage of the present research, as no other literature on hydrotherapy studies were found investigating predictors for functional disability in a group of patients with RA.

The main limitations

The researcher did not achieve the sample size for this study, which was to recruit 86 patients excluding six participants in the pilot study. Therefore, it could be claimed that this study might be underpowered to detect clinically significant differences between hydrotherapy and land therapy using the HAQ-DI score.

However, seventy participants were invited to take part in the study; 48 (68.6%) expressed an interest in taking part, 22 (31.4%) did not wish to take part, and gave

no clear reasons. Five (10.4%) of 48 were withdrawn from the study after they signed the data access sheet and agreed to participate and the reasons for that are shown (Figure 6.1, p.169). Finally, 43 (61.4%) participants completed the intervention. 15/43 dropped out at three-month follow up, and 24/43 dropped out at six-month follow up.

Unfortunately, we did not collect data regarding reasons as to why patients were not interested in the study because it would have been a great burden on the clinicians. Therefore, it is not known if the participation rate was more or less than might be expected. However, the feasibility and the clinical acceptability of hydrotherapy and land-therapy intervention was assessed from both recruitment rate and participation through the programme; this proved inconsistent, because of a significant shortage in follow-up periods but a high adherence rate in all sessions.

Another factor that might determine clinical acceptability is the inclusion of the views of participants before and after the programme. This is the main drawback of this study, as patient perception was not investigated. Patient perception should be evaluated by using qualitative techniques rather than quantitative techniques. Future research should advocate the use of the qualitative interviewing approach exploring the views of patients about their treatment.

The main reason for small sample sizes in experimental studies in medicine, as advanced by methodologists, is that publication bias is more serious in small-sample research than in studies involving large samples (Slavin & Smith, 2009). However, studies with small sample sizes tend to have much larger positive-effect

sizes than do studies with larger sample sizes (Slavin & Smith, 2009). Most researchers involving small trials are considered to be unethical because they expose participants to the burdens and risks of human research, with a limited chance to provide any useful answers (Bacchetti et al., 2005; Biau & Kernéis, 2008). However, it can be stated that any similarly sized RCT is likely to be underpowered and inadequate. Therefore, it is advisable that a more comprehensive study with a suitable sample size should be conducted with a less restrictive inclusion and exclusion criteria.

In spite of the small sample size of this study, multiple statistical tests were used in this thesis, not just the t-test. These are of value, because for instance using only the t-test is tedious when more than one group are present. Using all the data increases stability and increases the chances of type-1 error. Conversely, using a large number of comparisons leads to the fact that some findings may appear significant by chance, and all the other non-significant findings would be ignored in order to favour the positive one.

The follow-up time was too short, despite accounting for the non-attendance at follow-up appointments. Considering the type of disease (life-long), a longer follow-up time would have given more relevance to the data, which could give more validity to the findings.

The research was undertaken at a single centre (SRFT). Although attempts were made to determine the external validity of the findings by comparing the patients to a local regional centre and other published work, it is not known what the characteristics are of patients at other regional centres. Further multicentre work is

required and confirmation of these findings with large sample size in other settings would be valuable.

No data were found in the literature about the HAQ-GWB. Being the first to include an outcome measure does preclude discussion or comparison with other findings. Previous studies have used HAQ-DI to measure functional ability rather than physical function.

Although it was demonstrated that there were significant differences in most of the outcomes included in Study One, it is accepted that some of these outcomes will be more important than others. Results from a self-assessment questionnaire cannot always be guaranteed because there is no way of checking the quality of individual answers.

Outcome measures

All the outcome measures were chosen for this study because of their importance to patients and clinicians, their ease of use, their practicality in analysis, and because they had to have good reliability and validity for RA patients. The measures were indicated to detect any treatment effects and the resultant differences between the two groups. However, the researcher considers that some of these outcome measures may not be suitable to detect differences in exercise studies in chronic disease such as RA. The best example is EQ-5D three-level dimensions (EQ-5D 3L also called EQ-5D tariff). The EQ-5D tariff was used in Study One because it is general, simple, easy to use, short and it is often used in other studies. It is acknowledged that there are two other questionnaires used to

measure QoL. One is called 'EQ-5D 5L', which was developed in 2011 (after carrying out Study Three).

The second one is used specifically in RA and called rheumatoid arthritis quality of life (RAQoL) (De Jong et al., 1997). RAQoL, consisting of 29 questions, was too long and would have been more burdensome for participants if it had been included in the RCT Study One, as there were already two lengthy questionnaires in place. This is the reason for its exclusion here but in the future, it might be recommended for use.

Another limitation of the study is that it included patients with a normal score of psychological wellbeing, i.e. a HADs score of < 14 , which is the borderline between normal and a probable condition of anxiety-depression. Future research could target a specific group of patients, for example, excluding patients with a HAD score of >14 in order to evaluate the effectiveness of hydrotherapy on the symptoms of anxiety-depression in patients with RA.

In conclusion, there are strengths and limitations in this thesis. It is evident that the major strengths of these quantitative outcome measures lie in their ability to measure a wide range of essential parameters in patients with RA. These outcome measures such as HAQ-DI, HAQ_{VAS}, HAQ-GWB, RADAI and HADs could be used for clinical assessment of RA patients. However, it is envisaged that the limitations discussed could be addressed in future studies of RA patients.

10.4 Methodological quality of the RCT

The methodological quality of the RCT Study One scored 8 out of 10 on the PEDro scale of internal validity, which is regarded as high quality (Kollen et al., 2009; Maher et al., 2003; Moseley et al., 2002). This result was because Study One was randomised, used concealed allocation and blinded the researcher. However, there was no blinding during data collection in Study One for healthcare providers and participants, and this could have led to bias. This study design used single blinding due to the nature of the treatment, and although the same therapists did not treat patients in both groups, it was not possible for blinding to be carried out for both physiotherapist and participants.

In a study such as this, it is very hard to blind the physiotherapists and participants from the type of intervention they attend. If participants are not blinded, knowledge of group assignment can affect responses to the treatment received (Kendall, 2003). Participants who receive a new treatment that they know has been assigned to them might have positive expectations or might be more anxious. Those assigned to the standard treatment, however, might feel deprived or relieved. In both conditions, an awareness of what they are about to receive, and perceptions of that treatment might affect the psychological or physical responses of the participants (Ferrucci, et al., 2004; Kendall, 2003).

Awareness of treatment allocation can also affect compliance and retention of trial participants (Kendall, 2003). It might have been useful to obtain the views of therapists regarding the allocation of participants in order to assess the potential bias, as is carried out in many drug trials, but this was not done. The researcher

acknowledges the importance of blinding in a clinical study whenever possible, as it represents an essential, distinct aspect of RCTs.

10.5 Economic evaluation

This study provides valuable cost-effectiveness data comparing hydrotherapy with land therapy in RA patients. Along with Study One, this can be used in healthcare decision-making and service organisation. This study might provide an overview of important sources of health-economic information. This study is the first to examine the costs of hydrotherapy for patients with RA. Despite this, methodological weaknesses have been outlined in this economic trial. First, the full economic evaluation was only undertaken in the short term, that is, an eight weeks period between the baseline and two weeks post-intervention. There may still be important longer-term healthcare costs that have not been captured, such as extra GP, consultant and physiotherapy treatment.

Second, the accuracy of time spent with patients was not verified. We considered an average, standard cost for consultant time, GP time, physiotherapist and physiotherapy assistant time based on data from the Personal Social Services Research Unit (PSSRU) (Curtis, 2011). A different cost might have been found had we calculated individual direct and indirect cost of time.

It is recognised that appointment times or waiting times might take longer. In Study Three (p. 222), we did not consider sensitivity analysis according to grade and salary. This is because it is unlikely that clinicians at different grades would treat land-therapy and hydrotherapy patients. Finally, because there was no

difference in EQ-5D tariff between the two groups, it was not possible to calculate the cost per QALY, which eliminates the ability for comparisons to other studies.

10.6 Key learning from the research

Despite the study not producing the conclusion that was hoped for, a great many ideas have emerged from the findings. The ideas and focus the researcher had at the outset have been altered. The research started as very impersonal and scientific, but the participants and how they personally responded to treatment became a focus. Despite being given much support and help from the physiotherapists and the RA consultants, as well as having the co-operation of the participants, it was expected that the answers he had expected would be found without too many problems. However this was not to be the case; there were problems with recruiting the participants, then one of the hydrotherapy centres closed. There were many issues that were required by the ethics committee to change the study protocols, which led to the lengthy delay to start the study. In addition, many patients showed a lack of interest in returning for follow-up questionnaires.

This study reinforce the importance of early diagnosis of RA. The actual diagnosis is still under debate, which means that studies to define factors to give an accurate early diagnosis would be of benefit to the healthcare system and the patient. The early initiation of treatment, as it was discussed in Chapter 9, is also of great importance – if the treatment was initiated earlier, it would mean that the disease progression is most likely to be abated , which is so important for the patient and potentially may reduce healthcare costs.

Hydrotherapy once per week for six weeks improved physical function, psychological wellbeing and pain to those with RA. Not known is the optimal duration of treatment to give maximum benefit and whether this varies from patient to patient. Study One demonstrated short-term benefit but did not provide evidence of longer term benefit. It might be that longer-term effects are unlikely to be found due to the nature of the physiological and psychological effects of hydrotherapy. From the findings in this thesis, it is possible to appreciate how important it is to have long-term follow up. Not only has this study not been able to give definitive answers, but also the results are inconclusive.

It is apparent for the need to choose important outcome measures for patients, as well as interventions that can be easily applied without exerting pressure on or burdening patients. The external validity of any study also depends on whether the outcomes were clinically relevant. This can depend on subtle considerations, such as who actually measured the outcome, but is more often dependent on what was measured and when.

The association between disease activity indices and anxiety and depression is another factor that needs further research. There are few studies with this focus, but because RA is a long-term disease without much respite, there is a vital need to understand more about remitting disease activity and mitigating anxiety and depression to enhance QoL.

It became apparent how little health workers knew about the cost of treatments. Maybe if more was understood about costs, more could be put in place to help save money, or at least to know where and why it is being spent. This is an area,

mainly in RA hydrotherapy, that lacks enough research, and given the constraints of the NHS, it should be considered.

By carrying out this study, the researcher has, in his opinion, become more empathetic towards staff and patients, and has come to understand more about chronic illness and people. This research has provided a better understanding about RA patients and it is hoped that better care will result because of it. Finally, it is intended that in future colleagues have an appreciation about the finances involved in health services provision.

10.7 Implications and recommendations

10.7.1 Implications for practice

For clinicians: This research has established that hydrotherapy provides more successful short-term outcomes than land exercises for those with RA. All clinicians should be encouraged to explore the possibility of prescribing hydrotherapy for patients with RA. Communication between physiotherapy departments and GPs and consultants should increase the awareness of the benefits of hydrotherapy. An increased awareness might allow colleagues to target patients who might benefit from treatment.

There are no studies that have led to the creation of guidelines for the referral of RA patients to physiotherapy in general and hydrotherapy specifically. Referrals by rheumatologists are often on an unplanned basis (Hurley et al., 2002). For this reason, the referral processes may vary from unit to unit depending on timing and other reasons (Hurley et al., 2002). It is important for all RA patients to be given the opportunity to receive hydrotherapy, where possible.

For decision makers: This research has outlined the detailed expense and effectiveness of hydrotherapy over land therapy on a 4:1 basis. It should encourage the safe treatment of patients on the minimum of a 4:1 basis in those departments with pools. For those planning on building pools, it should justify the exploration of providing a large enough area for group therapy rather than on a 1:1 basis. For those intending on closing a pool, it might be more cost effective to keep it open if group therapy is feasible, as it is not known whether group land treatment is a cheaper or more effective option. Hydrotherapy can also be used for conditions other than RA.

Presently, it is only known that hydrotherapy is effective in the short term. It is not feasible to provide hydrotherapy ad infinitum, and other alternatives to attending hydrotherapy in the hospital must be considered once maximum improvement has been made.

For patients: Patients should be provided with enough information, based on current research, for them to understand the benefits of hydrotherapy and to make an informed choice when offered it or consider giving it up.

10.7.2 Implications for research

This is the first study that has investigated the economic evaluation of hydrotherapy for RA patients. Future studies should consider investigating the cost-effectiveness of hydrotherapy and the best aquatic exercise for RA patients in the longer term. It is not clear whether the short-term effects of hydrotherapy have long-term impacts on costs to the provider, the patient or society.

Using the findings of this research, there is a need for more work to be done in order to determine the effectiveness of hydrotherapy on disease activity, psychological aspects of RA and aspects of physical function, by utilising the accurate outcome measures involved. There is also a need for more adequately powered studies to determine the effectiveness of hydrotherapy.

It is acknowledged that there may be other factors associated with RA such as fatigue or grip strength that were not measured in Study One. However, in order for patients with this condition to receive appropriate treatment for their condition, the identified parameters (section 9.2.3.3, p.283) should be optimised in the future using other methodologies. Moreover, future research should examine the association of anxiety and/or depression with disease activity, and this should be measured by a self-administered questionnaire such as the RADAI.

Further research should examine the effects of hydrotherapy, not only comparing various interventions, but also other trials comparing interventions with a no-treatment control group. When possible, the beneficial effect of the aquatic environment should be considered as a confounder or effect modifier, and should be accounted for in the design of the study, although this has ethical implications.

Although short-term gains have been shown, it is not known how hydrotherapy affects locus of control. Some patients choose not to, or are unable to, continue water-based treatment independently. Other patients are advised or choose to continue water-based treatment by themselves, or in local groups. These water-based treatments can be in a hydrotherapy pool or local swimming pool at a

leisure centre. It is not known whether the same effects observed during hydrotherapy, will be replicated if they are continued as self-management.

10.8 Conclusion

Hydrotherapy for patients with arthritis is one of the oldest forms of therapy. Hydrotherapy has an important role in the management of RA and aims to maximise physical function and reduce functional disabilities. Study One found favourable evidence of the benefit of aquatic exercise when compared to the land exercises after six-week intervention period.

The scientific evidence from all three studies is valid because of the good methodological quality, adequate statistical analysis, and for the patient the use of essential outcome measures. It provides some evidence that compared to land therapy, hydrotherapy is more beneficial and cheaper for people with RA. As the cost of managing RA is high, further research is needed to determine the efficacy and CE of hydrotherapy, and to create appropriate intervention strategies to optimise the management of the physiotherapy service. Providing six sessions of hydrotherapy to RA patients is more effective than land-exercise therapy, and that it is less costly to the NHS than land-therapy.

The hypothesis: ‘There will be no significant difference in HAQ-DI score between hydrotherapy and land-therapy arms in patients with RA’ can be rejected.

PUBLICATIONS AND CONFERENCE PRESENTATIONS ORIGINATING FROM STUDY:

Al-Qubaeissy, K. Y., Fatoye, F. A., Goodwin, P. C. and Yohannes, A. M. (2013) 'The Effectiveness of Hydrotherapy in the Management of Rheumatoid Arthritis: A Systematic Review.' *Musculoskeletal Care*, 11(1) pp. 3-18.
<http://onlinelibrary.wiley.com/doi/10.1002/msc.1028/abstract;jsessionid=6DD654A89B3F2B75D8B380CD036A432C.d04t04?deniedAccessCustomisedMessage=&userIsAuthenticated=false>

CONFERENCES PRESENTATIONS AND POSTERS:

- Received the certificate of poster participation in RIHSC Conference, 2010;
- Attended the Annual Research Student Conference and gave a poster presentation, 27 January 2011;
- Award 2nd Prize in RIHSC Conference Poster, July 2011;
- Attended a conference for postgraduate researchers in science medicine in North West England, 4 July 2011;
- Delivered a proposal presentation (Medical rehabilitation: the effect of aquatic physiotherapy in RA patients) to all rheumatologists, medical staff and research nurses of the rheumatology department at the Kellgren Centre within Central Manchester University Hospitals, 3 August 2010;
- Delivered a proposal presentation (Medical rehabilitation: the effect of aquatic physiotherapy in RA patients) to all rheumatologists, rehabilitation and research staff at Salford Royal Foundation Trust, 20 April 2011;
- Delivered a proposal presentation (Medical rehabilitation: the effect of aquatic physiotherapy in RA patients) to all rehabilitation and research and development staff at Rehabilitation Unit 1 within Central Manchester Foundation Trust, 12 August 2010.

APPENDICES

Appendix 1: Letter to clinicians

Dear Colleagues:

May I introduce myself and the reason for my letter?

My name is Khamis Al-Qubaeissy; I have a higher diploma degree in Rheumatology and Medical Rehabilitation from College of Medicine/ Baghdad University. Now, I am a postgraduate student from Manchester Metropolitan University. I am writing on the recommendation of my Advisory team (Dr. Peter Goodwin, Dr Abebaw Yohannes and Dr Francis Fatoye) who suggested that I might contact you to discuss the possibility of collaborating with you and all outpatients Rheumatology clinicians on an upcoming research project. Currently I am conducting my PhD research in Medical rehabilitation of Rheumatoid Arthritis (RA). I will try to give you a brief outline of the proposed research. The research will focus on effects of Aquatic physiotherapy in RA. The effects of aquatic physiotherapy in RA has been investigated in previous studies, however, their findings are inconclusive and unclear.

The objectives of my current research are to determine the outcomes of Aquatic physiotherapy for improving pain, function and quality of life in patients with RA. Furthermore, investigate the effective role of Aquatic physiotherapy in terms of Health care utilisation in comparison with land therapy and usual care. In addition, to determine the cost effectiveness of combined Aquatic physiotherapy and usual treatment in RA. It is intended that this research will help all RA patients to develop an appropriate intervention method, which will help to prevent further damage of the joint or irreversible disability, and achieve maximum function with physical improvement.

This research will require the recruitment of 86 RA patients according to American College of Rheumatology (ACR) 1987 revised criteria. The choice of the candidates for this study will depend on the inclusion and exclusion criteria in order to avoid any risk and discomfort that might happen during research.

I have attached a flow chart, which outlines the research protocol, outcome measures and inclusion/exclusion criteria. We hope to involve several research sites across the Greater Manchester area in order to aid recruitment and ensure a representative patient sample. We are very interested in collaborating with yourself and all Rheumatologists in outpatients Rheumatology clinic and wonder if you would consider being involved in the study. If you have any questions or would like any further information, please do not hesitate to contact me. I look forward to hearing from you soon.

Khamis Al-Qubaeissy
Postgraduate Student

Appendix 2: Data Access Sheet

**Study Title: Medical rehabilitation: The effect of aquatic physiotherapy
in patients with Rheumatoid Arthritis**

Name: _____

Address: _____

Tel: Home _____ Mobile _____

I give permission

I do not give my permission

I would like more time before giving my permission

...for Khamis Al-Qubaeissy to contact me regarding the above study.

The best time to call is

am _____

pm _____

Signed: _____ Date: _____

Appendix 3: Patient information sheet

Version V

Date: 28/2/2011

Part 1.

1. Project Title.

Medical rehabilitation: the effects of aquatic physiotherapy (hydrotherapy) in patients with Rheumatoid Arthritis (RA).

2. Invitation paragraph

I would like to invite you to take part in a research study, which will be conducted by Mr. Khamis AL-Qubaeissy, a postgraduate researcher in Medical Rehabilitation in the Manchester Metropolitan University. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Feel free to talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.

- Part 2 gives you more detailed information about the conduct of the study.

Please ask me if there is anything that is not clear or if you would like more information.

Take time to decide whether you wish to take part.

3. What is the purpose of the study?

The main purpose of this research is to look at what happens when patients take part in aquatic physiotherapy (exercises in a warm water pool), we are interested how this will affect pain, movement and quality of life in patients with Rheumatoid Arthritis (RA), and we are interested in how much this treatment costs the NHS patients and employers. It is hoped that the results of this study will help clinicians to develop appropriate treatment for all patients with RA, to prevent further damage of the joint or irreversible disability, achieve maximum function, and ultimately improve quality of life. Patients might need other types of therapy in addition to drugs treatment to improve their general function, e.g. occupation therapy.

4. Why have I been chosen?

You have been chosen because you have a diagnosis of RA. The volunteers who take part in this study are screened and selected carefully by the treatment team involved in their treatment programme. It is anticipated that up to 86 volunteers will participate in this trial. During the trial, there is no need to withhold any type of treatment prescribed by your physician.

5. Do I have to take part?

Appendix 3 (continued)

Participation in the research is voluntary, and if you decide to participate, you will be given the information sheet and a consent form to read and keep, you will also be asked to sign a Data Information Sheet, which says you are happy for us to contact you. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

6. What will happen to me if I take part?

If you have decided to take part, then please read the following guidelines carefully:

- The study will recruit 86 patients with RA from the outpatient rheumatology clinic in Manchester Royal Infirmary.
- The research will last up to a maximum of 6-8 months.
- All volunteers will be divided into two groups: a group who exercise on land and in water, or a group who only exercise on dry land.
- All volunteers will be asked to complete some questionnaires, which are simple to fill out, and will take about 15 to 30 minutes. You will be asked to fill out the questionnaires before the study starts, then 6 weeks, 3 months and 6 months later. You should continue taking your usual medication during the study.
- If you are chosen to receive treatment on dry land you will be asked to attend the physiotherapy department where a physiotherapist will guide you through the best treatment for your needs.
- If you are chosen to exercise on land and in warm water, you will be asked to attend physiotherapy once a week for 6 weeks. As well as being guided through the best treatment for your needs, you will exercise in a warm pool for approximately 30 minutes following each physiotherapy appointment. This will be with two to three other patients and you will then spend 4-5 minutes relaxing afterwards.
- Your participation is voluntary; you are free to withdraw at any time, without giving a reason. If you agree to take part, then all details will be explained to you. We will ask you to sign a consent form. This will not affect any of the care you receive.
- One of our team will go through the information sheet with you and answer any questions you have and this should take about (20-30) minutes.
- If there is anything that is not clear please contact Mr. AL-Qubaeissy in the first instance (contact details below).
- Mr. Al-Qubaeissy will follow ethical and legal practice and all information about you will be handled in confidence.
- Your name will not be identified in any publication or thesis
- There are no restrictions on the type of clothing that you may wear.

Appendix 3 (continued)

- To maintain your privacy, only the clinical team from the physiotherapy department and Mr. Al-Qubaeissy will be present during most of the trial. Occasionally Mr. Al-Qubaeissy academic supervisors may be present.

7. What do I have to do?

During the trial, you will be guided throughout the procedures. A thorough explanation will be given at each session attended.

8. What is the procedure that is being tested?

The nature of the trial will involve comparing usual treatment (control group), physiotherapy on dry land, with the usual therapy plus an aquatic session in RA (intervention group). The intervention group will therefore receive sessions of aquatic physiotherapy (exercises in a warm pool) led by senior physiotherapists (at a water temperature of between 34-36° Celsius). Every aquatic physiotherapy session includes between 2-4 patients per session because of the size of the aquatic therapy pools. Before the session, participants will perform warm up exercise for 10 minutes in the water while the main exercises will focus on joints movement, muscle strength and functional activity. Patients will receive a 30-minute session of hydrotherapy once weekly for 6 weeks. Each session will take place in the aquatic pool in the Manchester Royal Infirmary under supervision of highly experienced physiotherapists. The design of the exercise programme is standardized in consultation with the physiotherapists. The therapist in response to individual ability will adjust patient progression.

9. What are the possible disadvantages and risks of taking part?

There will be no disadvantages taking part in this study. Patient's safety is paramount for this study. Therefore, we take the following action where appropriate:

- a) Patients who experience excessive fatigue during exercise in the aquatic pool will be allowed to stop whenever they feel tired.
- b) Exclusion criteria will be employed to prevent patients being included that will not benefit from, or will be at risk from entering the pool, for example: those with chlorine sensitivity, epilepsy or hydrophobia. If a patient develops a sudden adverse reaction, for example chlorine sensitivity, treatment will be stopped. Advice will be given to the patient to see their GP to discuss chlorine sensitivity. As patients have been referred to physiotherapy by their consultant rheumatologist and are deemed suitable for aquatic physiotherapy, no extra burden for the patients by attending treatment is anticipated.
- c) In case of emergency, the hospital's emergency protocol will be adopted; This procedure is practiced 3-4 times annually, for example: testing of the emergency alarm, response time and use of emergency pool evacuation equipment.

Appendix 3 (continued)

D) For safety, if patients do not speak English, it will be a requirement that a translator is present in the pool and when completing the questionnaires.

10. What are the possible benefits of taking part?

This study is of an experimental nature, and we cannot promise the study will help you, it is hoped that the results of this study will help clinicians to develop appropriate interventions for patients with RA, to prevent further damage of the joint or irreversible disability, pain and achieve maximum function and ultimately improve quality of life. Patients need additional therapy to drugs for longer-term effects. Water is regarded as an appropriate environment for treating RA patients as warm water relaxes tense muscles and increases blood flow to the tissues.

11. What happens when the research study ends?

When the study comes to its natural end, should patients still require physiotherapy they will still be able to attend either land based treatment or aquatic physiotherapy as is deemed appropriate to their ongoing care. This can be discussed with the physiotherapist.

12. What if there is a problem?

If you need to seek clarification about this study, please contact Mr. Khamis AL-Qubaeissy or his Academic Supervisor ([contact details below](#)) who will do their best to answer your questions

If you have a concern about any aspect of the conduct of this study, please contact either the University or the NHS Trust below.

Central Manchester University Hospitals NHS Foundation Trust – Dr Lynne Webster, Head of Research Office, 1st Floor Postgraduate Centre, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL. Tel: 0161 276 4125, lynne.webster@cmft.nhs.uk
Manchester Metropolitan University – Professor Valerie Edwards-Jones, Director of Research, Research and Enterprise Services, Ormond Building, Lower Ormond Street, Manchester M15 6BX. Tel: 0161 247 1025

In the event of any complaint about the way you have been dealt with during the study or any possible harm you might suffer, please refer to the NHS Patient Advice & Liaison (PALS) Team.

How to contact the PALS team - Telephone: 0161 276 8686, E-mail: pals@cmft.nhs.uk

Please note that you may withdraw from the study at any time during the trial without any effect on your care and treatment. Every effort will be made to ensure your continued comfort and safety.

Appendix 3 (continued)

In the event that something does go wrong, you are harmed during the research study, and this is due to negligence of the researchers or clinical team, both the Manchester Metropolitan University and Central Manchester University Hospitals NHS Foundation Trust maintain insurance in the event of such a claim due to negligence of their students and employees. You may have grounds for legal action; however, you may have to pay your legal costs. Further information can be provided via the PALS team within the NHS or via the Manchester Metropolitan University through their Institutional contact.

13. Will my taking part in the study be kept confidential?

If you join the study, all the information about your participation in this study will be kept confidential. The lead researcher will look at some parts of your medical records and the data collected for the study. Authorised people may also look at them from Central Manchester University Hospitals NHS Foundation Trust to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site. Your details will not be passed on to a third party and no data will be transferred for the purpose of processing or analysing outside the European Economic Area. All names will be replaced with codes so that individuals cannot be identified. We intend to publish the results of the study, that is, which treatment was the most successful, but names or details of individuals will not be published.

14. Contact Details:

For more information, please refer to:

Khamis AL-Qubaeissy, Doctoral Researcher/Medical Rehabilitation,

Manchester Metropolitan University,

Elizabeth Gaskell Campus, Hathersage Road,

Manchester. M13 0JA.

Tel: 07588695372, email: 09981701@stu.mmu.ac.uk

Academic Supervisor:

Dr. Peter Goodwin

Manchester Metropolitan University,

Elizabeth Gaskell Campus,

Hathersage Road,

Manchester. M13 0JA.

Tel: 0161 247 2941, email p.goodwin@mmu.ac.uk

This completes Part 1 of the Information Sheet.

Appendix 3 (continued)

If the information in Part one has interested you and you are considering participation, please continue to read the additional information in Part two before making any decision.

Part 2:

15. What if relevant new information becomes available?

A letter explaining such information, when it becomes available would be given to the subjects and you would be encouraged to discuss the implications of such with the research team if you so wished. If new data becomes available that would affect your participation in the study you will be asked to re-consent.

16. What will happen if I do not want to carry on with the study?

If you withdraw from the study, we would like to use the data collected up to your withdrawal, or you can choose to have your data withdrawn from the study also.

17. Involvement of the General Practitioner/Family doctor (GP)

If you are recruited in the research, then a letter will be sent to your G.P. notifying him/her of your desire to partake in the trial and if they have, any concerns then the G.P. should let me know.

18. What will happen to the results of the research study?

The results will be used in a PhD thesis, and may be published in a scientific journal or presented at a scientific conference.

19. Who is organising and funding the research?

The project is part of a PhD and no funding has been sought for this trial.

20. Who has reviewed the study?

Finally, before any research goes ahead, all research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favorable opinion by Research Ethics Committee. Central Manchester University Hospitals NHS Foundation Trust has reviewed and authorised the study and the study has been given a favorable ethical opinion by the Manchester Metropolitan University Research Ethics Committee.

Thank you for reading this – please ask

Appendix 4: Consent form

Date:...../...../.....

Version V

Centre Number:

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: **Medical rehabilitation: The effects of aquatic physiotherapy
in patients with Rheumatoid Arthritis (RA).**

Name of Researcher: **Khamis Al-Qubaeissy**

Please initial
box

1. I confirm that I have read and understand the information sheet dated.....28/02/2011
(version..V.....) for the above study. I have had the opportunity to consider the information,
ask questions and have had these answered satisfactorily.

☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time
without giving any reason, without my medical care or legal rights being affected.

☐

3. I understand that relevant sections of my medical notes and data collected during the study,
may be looked at by individuals.

☐

4. I agree to my GP being informed of my participation in the study.

☐

5. I agree to take part in the above study.

☐

Name of Patient

Date

Signature

Name of Person **Khamis**
taking consent **Al-Qubaeissy**

Date

Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Appendix 5: Health Assessment Questionnaire

Medical Rehabilitation: The effects of Aquatic Physiotherapy in patients with
Rheumatoid Arthritis (RA)

Patient Id:

Date:



The STANFORD HEALTH ASSESSMENT QUESTIONNAIRE ©
Stanford University School of Medicine, Division of Immunology & Rheumatology

HAQ Disability Index:

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty ⁰	With SOME difficulty ¹	With MUCH difficulty ²	UNABLE to do ³
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Shampoo your hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ARISING				
Are you able to:				
-Stand up from a straight chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Get in and out of bed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EATING				
Are you able to:				
-Cut your meat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Lift a full cup or glass to your mouth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Open a new milk carton?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Climb up five steps?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please check any **AIDS OR DEVICES** that you usually use for any of these activities:

- | | |
|-------------------------------------|---|
| <input type="checkbox"/> Cane | <input type="checkbox"/> Devices used for dressing (button hook, zipper pul |
| <input type="checkbox"/> Walker | long-handled shoe horn, etc.) |
| <input type="checkbox"/> Crutches | <input type="checkbox"/> Built up or special utensils |
| <input type="checkbox"/> Wheelchair | <input type="checkbox"/> Special or built up chair |
| | <input type="checkbox"/> Other (Specify: _____) |

Please check any categories for which you usually need **HELP FROM ANOTHER PERSON:**

- | | |
|--|----------------------------------|
| <input type="checkbox"/> Dressing and Grooming | <input type="checkbox"/> Eating |
| <input type="checkbox"/> Arising | <input type="checkbox"/> Walking |

Appendix 5 (continued)

Please check the response which best describes your usual abilities **OVER THE PAST WEEK**:

	Without ANY difficulty ⁰	With SOME difficulty ¹	With MUCH difficulty ²	UNABLE to do ³
HYGIENE				
Are you able to:				
-Wash and dry your body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Take a tub bath?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Get on and off the toilet?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Bend down to pick up clothing from the floor?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
GRIP				
Are you able to:				
-Open car doors?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Open jars which have been previously opened?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Turn faucets on and off?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ACTIVITIES				
Are you able to:				
-Run errands and shop?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Get in and out of a car?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-Do chores such as vacuuming or yardwork	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please check **any AIDS OR DEVICES** that you usually use for any of these activities:

<input type="checkbox"/> Raised toilet seat	<input type="checkbox"/> Bathtub bar
<input type="checkbox"/> Bathtub seat	<input type="checkbox"/> Long-handled appliances for reach
<input type="checkbox"/> Jar opener (for jars previously opened)	<input type="checkbox"/> Long-handled appliances in bathroom
	<input type="checkbox"/> Other (Specify: _____)

Please check **any categories** for which you usually need **HELP FROM ANOTHER PERSON**:

<input type="checkbox"/> Hygiene	<input type="checkbox"/> Gripping and opening things
<input type="checkbox"/> Reach	<input type="checkbox"/> Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN

No Pain Severe Pain

HAQ_{VAS}

0 100

Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line.

Very Well Very Poor

HAQ-GWB

0 100

Appendix 6: EQ-5D 3L (EQ-5D tariff)

Medical rehabilitation: The effects of aquatic physiotherapy
in patients with Rheumatoid Arthritis.

Baseline measurement

Patient Identification Number for this trial:

Date:...../...../.....

EQ-5D (UK English version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

Appendix 7: EQ-5D_{VAS}

Medical rehabilitation: The effects of aquatic physiotherapy
in patients with Rheumatoid Arthritis.

Patient Identification Number for this trial:

Date: / /

EQ-VAS

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**

Best
imaginable
health state

100

90

80

70

60

50

40

30

20

10

0

Worst
imaginable
health state

Appendix 8: Rheumatoid Arthritis Disease Activity Index (RADAI)

Medical Rehabilitation: the effects of aquatic physiotherapy in patients with Rheumatoid Arthritis (RA)

RADAI® PATIENT QUESTIONNAIRE

Patient Id:

PLEASE ANSWER THESE QUESTIONS ABOUT YOUR ARTHRITIS

1) In general, how active has your arthritis been over the last 6 months?

Please mark the degree of activity with a cross on the rating scale below.

not active at all	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	extremely active
-------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	------------------

2) In terms of joint tenderness and swelling, how active is your arthritis today?

Please mark the degree of activity with a cross on the rating scale below.

not active at all	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	extremely active
-------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	------------------

3) How much arthritis pain do you feel today?

Please mark the degree of pain with a cross on the rating scale below.

no pain at all	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	unbearable pain
----------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------------	-----------------

4) Were your joints stiff when you woke up today?

- ☐ No
- ☐ Yes If yes, how long did this stiffness last today?
Please mark the duration of stiffness with a cross.
- ☐ Less than 30 minutes
- ☐ 30 minutes to 1 hour
- ☐ 1 - 2 hours
- ☐ 2 - 4 hours
- ☐ More than 4 hours
- ☐ All day

1

RADAI - UK/English - Final version - 29 May 07 - Mapi Research Institute.
t:\institucultadapi\project\4121\study4121\final_versions\radaiukq.doc-29/05/2007

Appendix 8 (continued)

5- Please indicate with a cross the amount of **pain** you are having **today** in each of the joint areas listed below

	Left Side					Right Side			
	none	mild	mode- rate	severe		none	mild	mode- rate	severe
Shoulder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	Shoulder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Elbow	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	Elbow	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Wrist	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	Wrist	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Fingers	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	Fingers	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Hip	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	Hip	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Knee	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	Knee	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ankle	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	Ankle	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Toes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	Toes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Appendix 9: DAS28 form

Patient name.....Date of Birth-.....-.....

Observer name.....Date-.....-.....

	Left		Right	
	Swollen	tender	Swollen	Tender
Shoulder				
Elbow				
Wrist				
MCP 1				
2				
3				
4				
5				
PIP 1				
2				
3				
4				
5				
Knee				
Subtotal				
Total	swollen		Tender	

No disease activity

high disease activity

Swollen (0-28)

Tender (0-28)

ESR

VAS disease activity (0-100mm)

DAS28 = $0.56 \cdot \sqrt{(t28)} + 0.28 \cdot \sqrt{(sw28)} + 0.70 \cdot \ln(ESR) + 0.014 \cdot VAS$

--

Appendix 10: Hospital Anxiety Depression scale (HADs)

Medical Rehabilitation: the effects of aquatic physiotherapy in
patients with Rheumatoid Arthritis (RA).

Patient ID:

Date:...../...../.....

HAD Questionnaire

Doctors are aware that emotions play an important role part in most illnesses. If your doctor knows about these feelings he will be able to help you more. This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate.

Tick one box only in each section

1. I feel tense or "wound up":

Most of the time..... ☐
A lot of the time..... ☐
Time to time, occasionally..... ☐
Not at all..... ☐

2. I still enjoy the things I used to enjoy:

Definitely as much..... ☐
Not quite so much..... ☐
Only a little..... ☐
Hardly at all..... ☐

3. I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly..... ☐
Yes, but not too badly..... ☐
A little, but it does not worry me.... ☐
Not at all..... ☐

4. I can laugh and see the funny side of things:

As much as I always could..... ☐
Not quite so much now..... ☐
Definitely not so much now..... ☐
Not at all..... ☐

5. Worrying thoughts go through my mind:

A great deal of the time..... ☐
A lot of the time..... ☐
From time to time but not too often ☐
Only occasionally..... ☐

6. I feel cheerful:

Not at all..... ☐
Not often..... ☐
Sometimes..... ☐
Most of the time..... ☐

7. I can sit at ease and feel relaxed:

Definitely..... ☐
Usually..... ☐
Not often..... ☐
Not at all..... ☐

8. I feel as if I am slowed down :

Nearly all the time..... ☐
Very often..... ☐
Sometimes..... ☐
Not at all..... ☐

9. I get a sort of frightened feeling like "butterflies" in the stomach :

Not at all..... ☐
Occasionally..... ☐
Quite often..... ☐
Very often..... ☐

10. I have lost interest in my appearance:

Definitely..... ☐
I don't take so much care as I should..... ☐
I may not take quite as much care..... ☐
I take just as much care as ever..... ☐

11. I feel restless as if I have to be on the move:

Very much indeed..... ☐
Quite a lot..... ☐
Not very much..... ☐
Not at all..... ☐

12. I look forward with enjoyment to things:

As much as ever I did..... ☐
Rather less than I used to..... ☐
Definitely less than I used to..... ☐
Hardly at all..... ☐

13. I get sudden feeling of panic:

Very often indeed..... ☐
Quite often..... ☐
Not very often..... ☐
Not at all..... ☐

14. I can enjoy a good book or radio or TV programme:

Often..... ☐
Sometimes..... ☐
Not often..... ☐
Very seldom..... ☐

Appendix 11: Treatment Strategy form

Participant number:									
Physiotherapy diagnosis:									
Aims of intervention:	1] 2] 3] 4] 5]								
Short term goals:	1] 2] 3]								
Long term goals:	1] 2] 3]								
Category of intervention	Interventions in this category	Physiotherapy sessions (tick RX provided)							
		1	2	3	4	5	6	7	8
Mobility functional treatment	Walking aid assessment								
	Gait re-education								
	Stairs								
	Activities of daily living assessment								
	Splinting								
Education and advice	Flare-up management advice								
	Return to activity and work advice								
	Education group attendance								
	Pacing advice								
	Joint protection advice								
General rehabilitation	Progression of exercises								
	Graded functional exercises								
	Paced increase in activity								
	General fitness exercises								
	General strength training								
	Low intensity exercises								
	High intensity exercises								
	Short and long term goal setting								

Appendix 11 (continued)

Home exercises/programme	Tailored programme								
	Generalised exercise programme								
	Core stability								
	Range of movement exercises								
	Strengthening exercises								
	Heat/cold advice								
Pain relief	How to manage flare-ups								
	Wax baths								
	TENS								
	Acupuncture								
	Other electrotherapy								
Hydrotherapy exercises	Range of movement								
	Sustained stretches								
	Core stability exercises								
	Balance exercises								
Land Exercise:	Range of movement								
	Strengthening								
	Fitness Exercises								
	Gym-based group exercise								

Appendix 12: Hydrotherapy and Home exercise programme

[(Salford Royal Foundation NHS Trust, 2007) with permission]

Home exercise programme

Stretching exercises

Range of movement exercises

Fitness exercises

Home exercises start in form of range of movement to each part of body such as neck, shoulder, hip joints, feet, ankles, wrists, fingers and back.

Warm-up start routinely for 2-3 minutes in order to increase body temperature and heart rate (cardiovascular fitness). This started by marching on the spot, lifting knee high and swinging arms. Then step touch to the left and right, keep good pacing going.

Warm-up exercise



After that, start **stretching exercises**. It is recommended that all these exercises should be done slowly. Start with about five repetitions and build up the number gradually. If the patients have more pain either in the muscles or in the joints, stop. We recommend that you hold the position for 5–10 seconds. Do twice daily.

Stretching exercises for knee joints start as

Sit on edge of table or bed. Cross your ankles over. Push front leg backwards and back leg forwards against each other until the thigh muscles become tense. Hold for 10 seconds, and then relax. Switch legs and repeat.

Sit on edge of table or bed, keeping an upright posture with feet on the floor. Place weights around ankles or feet. Straighten one knee fully. Hold, and then slowly lower.

If the knee is hot or swollen, do not use weights.

Appendix 12 (continued)

For wrist joints, stretching start as

- 1) Place your left hand face down on the table and lift the fingers up away from the table.
- 2) Place your other hand across the knuckles at 90° and with your right hand, push down as the left hand tries to pull up.
- 3) Feel the muscles of your forearms contracting. Swap hands and repeat.

For finger stretching start as:

- 1) Begin with palm of your hand on a towel on a table, fingers apart.
- 2) Pull fingers together by pressing your hand down into the table and bunching up the towel between your fingers.

For Arm stretching start as Arms

- 1) Stand with arm straight, bend elbow, and then straighten out again. (Hold a weight in your hand such as a bag of sugar or a potato)
- 2) Stand with a weight in each hand, or use wrist weights. Raise your arms overhead as far as you can and slowly lower.
- 3) Stand with a weight in each hand, or use wrist weights. Place your arms by your sides. Slowly lift arms away from your body, keeping the elbows straight. Hold for 5 seconds and slowly lower.
- 4) Breathe steadily as you exercise. It is normal to feel muscle ache but stop if you get any lingering joint pain.
- 5) For range of movement should hold the stretch for about 5–10 seconds, then relax and repeat the movement 5–10 times. Do twice daily. If the joints are especially hot and swollen do these exercises gently and only do five repetitions once a day.

Neck

- 1) Sit with good posture, turn head to the right and then left slowly.
- 2) Sit or stand with good posture. Lower your chin to your chest, and then return to starting position
- 3) Sit or stand with good posture. Keeping your head level, pull your chin back. Relax, and then repeat.

Stop if you feel dizzy doing any of these exercises.

Shoulders

- 1) Stand with your arms relaxed at your sides.
- 2) Raise arms as far as you can.
- 3) Place hands behind head, then behind back.
- 4) Lie on your back. Raise arms overhead as far as you can.

Appendix 12 (continued)

Hips

- 1) Sit with knees bent and feet together as shown. Press knees down towards the floor using hands as needed.
- 2) Alternatively lie on your back and part your knees, keeping your feet together.
- 3) Lie on your back. Pull each knee in turn to chest, keeping the other leg straight.

Feet and ankles

- 1) Bend ankle up towards your body as far as possible. Now point toes away from your body.
- 2) Move your ankle around slowly in a large circle. Repeat in the opposite direction.

Fingers

- 1) Make a fist, and then straighten fingers.
- 2) Bend first two joints of your fingers down as shown, and then straighten again.

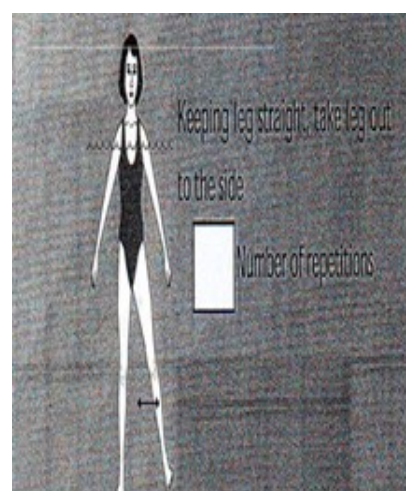
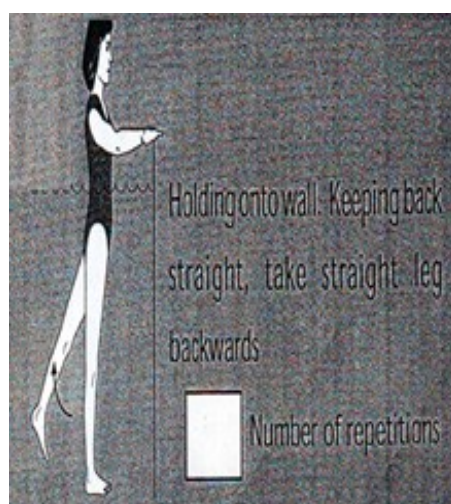
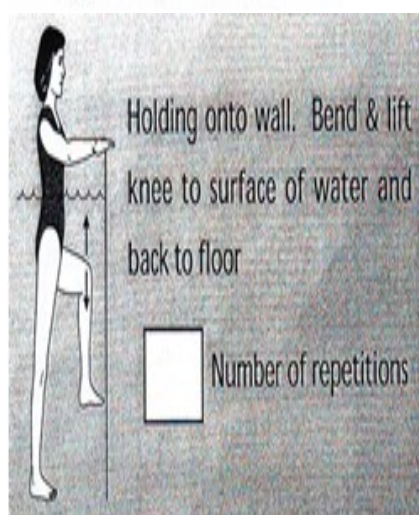
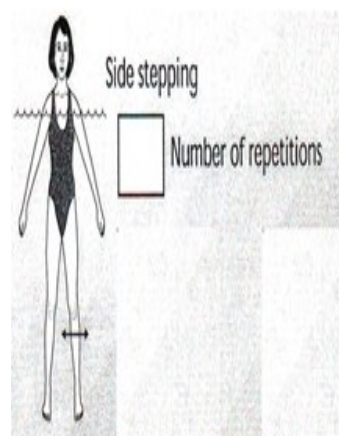
Back

- 1) Lie on your back, hands behind your head (or by your side if your shoulders are painful). Bend your knees and, keeping your feet to the floor, roll your knees to one side slowly. Hold this position for 10 seconds. Repeat this three times for each side.
- 2) Lie on your back. Bring one knee up and pull it gently to the chest. Push your back into the floor when doing this exercise. Hold, and then swap legs.
- 3) Straighten arms to press trunk upwards, letting hips sag to the floor.
Not recommended for people with rheumatoid arthritis who have wrist pain.
- 4) Place hands on hips as shown and bend slowly to one side until you feel a stretch. Hold, and then repeat on the other side.

Appendix 12 (continued)

Hydrotherapy programme

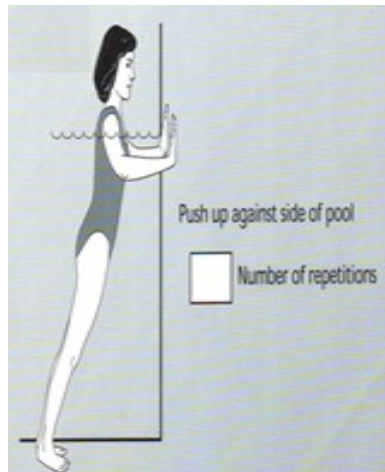
Warm up exercise in form of walking in the pool and sidestepping, knee to chest walking / heel to bottom walking, hip abduction / adduction & flexion / extension.



Appendix 12 (continued)

Sustained Stretching exercises: included

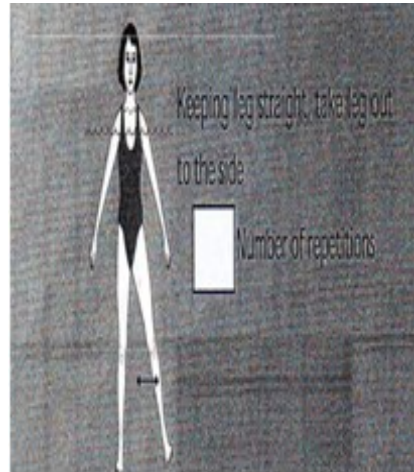
Upper limb stretches for rhomboids muscles, pectorals, deltoid, biceps, and triceps.



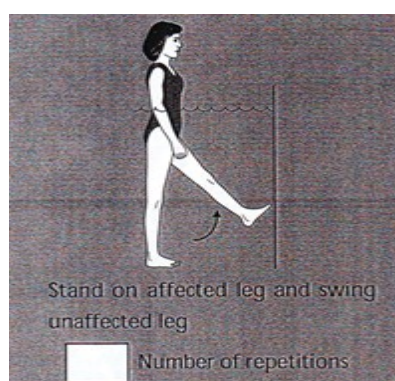
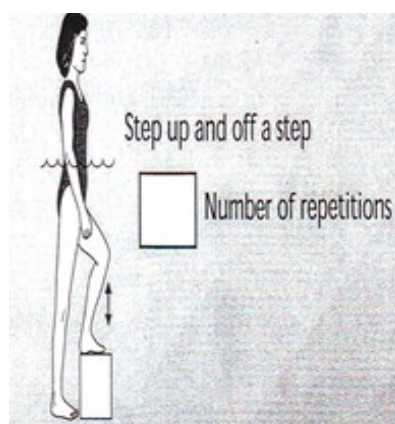
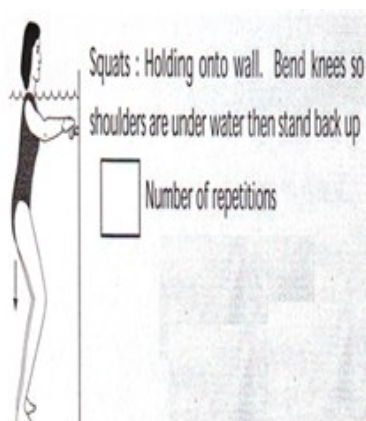
Lower limb stretches for gastrocnemius, soleus, hamstrings, hip-abduction, quadriceps

Lower Limb Buoyancy Assistance/Buoyancy Resistance: Straight Leg Raising as hamstring stretch.

Lower Limb hip Medial Rotation / Lateral Rotation in standing with woggle.



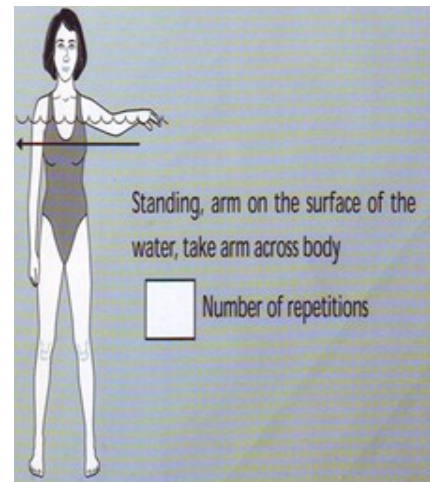
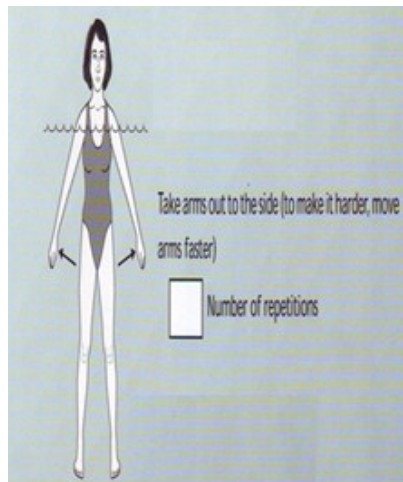
Appendix 12 (continued)



Range of movement: in addition to usual movement in the pool for knee to chest, heel to bottom, hip abduction and adduction, hip flexion and extension, there are many activities for range of motion exercises included:

- a) Breast stroke arms with floats.
- b) Lumbar extensions: rotation in corner.
- c) Extension/flexion side flexion at wall.
- d) Thoracic rotation with woggle.
- e) Upper limb buoyancy assistant: Gleno-Humeral Joint flexion / abduction.
- f) Hands on poolside horizontal flexion stretch.
- g) Hands behind back stretch with dumbbells.
- h) Lower Limb Buoyancy Assistant/Buoyancy Resistant: abduction as adductor stretch / muscle strengthening.
- i) flexion/extension as extensor/flexor stretch muscle strengthening.

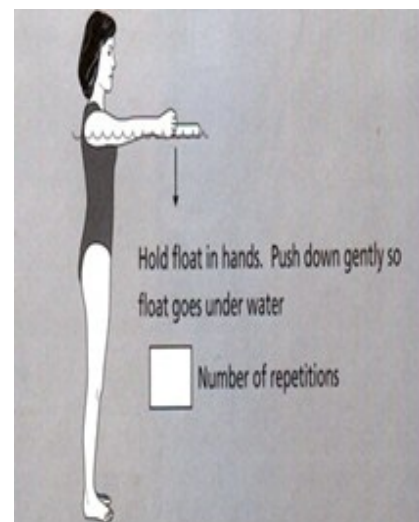
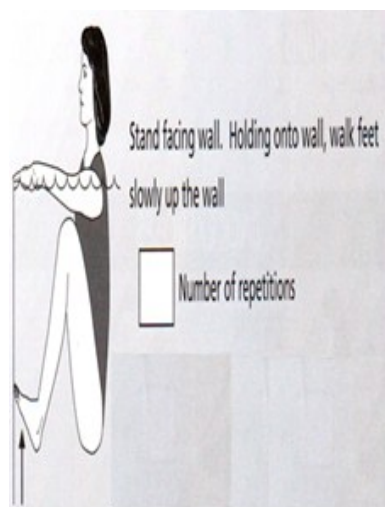
Appendix 12 (continued)



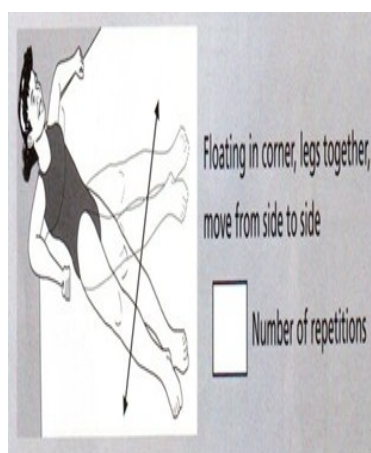
Trans -abdominals with float / woggle

Rowing with woggle forwards / backwards

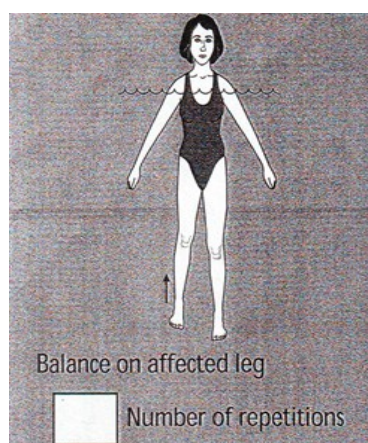
Supine floats work: cycling / hip abduction / knee rolling / Lumber Side Flexion.



Appendix 12 (continued)



Balance exercises: included walking / side stepping



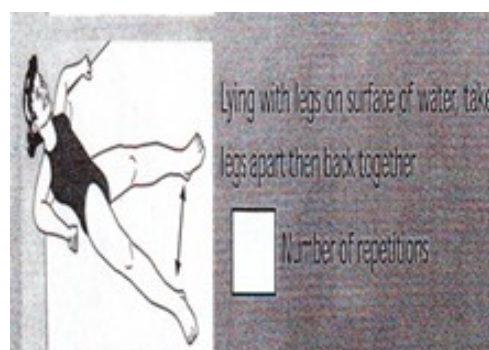
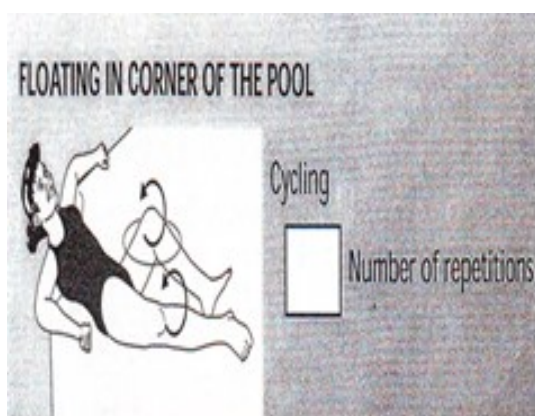
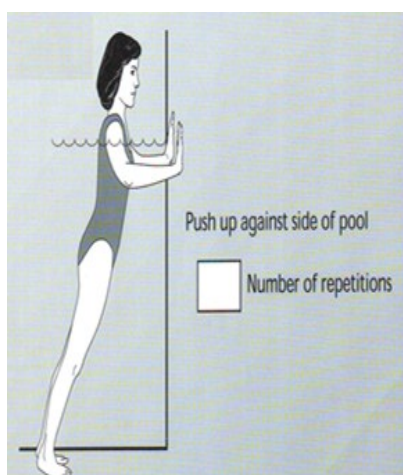
Proprioception: included walking on oblong floats and Walking against turbulence.

7) **Muscle strengthening:** included the following exercises:

- a) Elbow curls with dumbbells
- b) Upper Limb Buoyancy Resistance: Gleno-humeral Joint flexion / extension with bats or gloves.
- c) Gleno-humeral Joint abduction / adduction with bats or gloves.
- d) Elevation / depression with float or woggle.
- e) Protraction / retraction with float or woggle.
- f) Shoulder adduction / extension with dumbbells / bats.
- g) Elbow flexion / extension muscle strengthening with dumbbells / bats.
- h) Elbow flexion / extension with bats or gloves.

Appendix 12 (continued)

- i) Lower Limb Buoyancy Resistance/Buoyancy Assistance abduction as adductor stretch muscle strengthening.
- j) flexion/extension as extensor/flexor stretch muscle strengthening.
- k) Lower limb buoyancy resistance hip/knee extension with float / woggle.
- l) Step upside / eccentric step-downs.
- m) Heel raises.
- n) Drag ring walking / leg swings.



Cool down: include walking in the pool and sidestepping, knee to chest walking / heel to bottom walking, hip abduction / adduction & flexion / extension

Appendix 13: Land and home exercise programme

[(Salford Royal Foundation NHS Trust, 2007) with permission]

Home exercise: included

Stretching exercises

Range of movement exercises

Fitness exercises

Gym-based exercises (land): includes

- A) Squats
- B) Abdominals
- C) Shuttle walk or run, or treadmill
- D) Press-ups
- E) Star steps and jumps
- F) Arm exercises
- G) Step-ups
- H) Back exercises

Home exercises start in form of range of movement to each part of body such as neck, shoulder, hip joints, feet, ankles, wrists, fingers and back. **Warm-up** start routinely for 2-3 minutes in order to increase body temperature and heart rate (cardiovascular fitness). This started by marching on the spot, lifting knee high and swinging arms. Then step touch to the left and right, keep good pacing going.

Warm-up exercise



After that, start **stretching exercises**. It is recommended that all these exercises should be done slowly. Start with about five repetitions and build up the number gradually. If the patients have more pain either in the muscles or in the joints, stop. We recommend that you hold the position for 5–10 seconds. Do twice daily.

Stretching exercises for knee joints start as

Sit on edge of table or bed. Cross your ankles over. Push front leg backwards and back leg forwards against each other until the thigh muscles become tense. Hold for 10 seconds, and then relax. Switch legs and repeat.

Appendix 13 (continued)

Sit on edge of table or bed, keeping an upright posture with feet on the floor. Place weights around ankles or feet. Straighten one knee fully. Hold, and then slowly lower.

If the knee is hot or swollen, do not use weights.

For wrist joints, stretching start as

- Place your left hand face down on the table and lift the fingers up away from the table.
- Place your other hand across the knuckles at 90° and with your right hand, push down as the left hand tries to pull up.
- Feel the muscles of your forearms contracting. Swap hands and repeat.

For finger stretching start as:

- Begin with palm of your hand on a towel on a table, fingers apart.
- Pull fingers together by pressing your hand down into the table and bunching up the towel between your fingers.

For Arm stretching start as Arms

- Stand with arm straight, bend elbow, and then straighten out again. (Hold a weight in your hand such as a bag of sugar or a potato)
-
- Stand with a weight in each hand, or use wrist weights. Raise your arms overhead as far as you can and slowly lower.
- Stand with a weight in each hand, or use wrist weights. Place your arms by your sides. Slowly lift arms away from your body, keeping the elbows straight. Hold for 5 seconds and slowly lower.
- Breathe steadily as you exercise. It is normal to feel muscle ache but stop if you get any lingering joint pain.
- For range of movement should hold the stretch for about 5–10 seconds, then relax and repeat the movement 5–10 times. Do twice daily. If the joints are especially hot and swollen do these exercises gently and only do five repetitions once a day.

Neck

- 1) Sit with good posture, turn head to the right and then left slowly.
 - 2) Sit or stand with good posture. Lower your chin to your chest, and then return to starting position.
 - 3) Sit or stand with good posture. Keeping your head level, pull your chin back. Relax, and then repeat.
- Stop if you feel dizzy doing any of these exercises.

Appendix 13 (continued)

Shoulders

- 1) Stand with your arms relaxed at your sides.
- 2) Raise arms as far as you can.
- 3) Place hands behind head, then behind back.
- 4) Lie on your back. Raise arms overhead as far as you can.

Hips

- 1) Sit with knees bent and feet together as shown. Press knees down towards the floor using hands as needed.
- 2) Alternatively lie on your back and part your knees, keeping your feet together.
- 3) Lie on your back. Pull each knee in turn to chest, keeping the other leg straight.

Feet and ankles

- 1) Bend ankle up towards your body as far as possible. Now point toes away from your body.
- 2) Move your ankle around slowly in a large circle. Repeat in the opposite direction.

Fingers

- 1) Make a fist, and then straighten fingers.
- 2) Bend first two joints of your fingers down as shown, and then straighten again.

Back

- 1) Lie on your back, hands behind your head (or by your side if your shoulders are painful). Bend your knees and, keeping your feet to the floor, roll your knees to one side slowly. Hold this position for 10 seconds. Repeat this three times for each side.
- 2) Lie on your back. Bring one knee up and pull it gently to the chest. Push your back into the floor when doing this exercise. Hold, and then swap legs.
- 3) Straighten arms to press trunk upwards, letting hips sag to the floor. Not recommended for people with rheumatoid arthritis who have wrist.
- 4) Place hands on hips as shown and bend slowly to one side until you feel a stretch. Hold, and then repeat on the other side.

Appendix 13 (continued)

**For gym-based group exercises, circuit exercises, 2 minutes per station,
Exercises of**

Squats: this type of exercise help in lifting and bending through strengthen the powerful leg muscles in order to improve functional rehabilitation, muscle strength, core stability and balance.

Intensity level 1 – sit to stand. Stand straight with your feet shoulder width apart. Slowly squat to a sitting position on the chair. Then stand, and repeat. Remember to tighten your abdominal muscles

Intensity level 2 – squats. Squat to the level of the chair but stand again without sitting down. Remember to tighten your abdominals

Intensity level three – squat and hold. Squat to the level of the chair but without sitting down. Hold squat position just above the chair for 5 seconds before standing again. Remember to tighten your abdominal muscles



Abdominals: to improve core-stability and muscle strengthening by strengthen muscles of stomach, which maintain the posture.

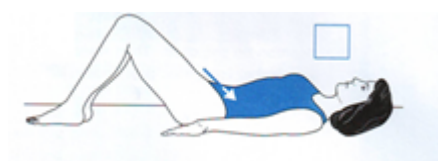
Intensity level 1 – Pelvic tilt and abdominal hollowing. Lie on your back with knees bent and feet flat on the floor. Rest your hands by your side. Perform a pelvic tilt by pulling your stomach in, pressing the small of your back into the floor so that your pelvis tilts backwards and your groin lifts upwards.

Intensity levels 2 – Pelvic tilt and curl to knees. Lie on your back with knees bent and feet flat on the floor. Place your hands on your thighs. Perform a pelvic tilt. Next, lift your head and shoulders to look between your knees. At the same time, slide your hands up your knees to touch your knees. Make sure you tuck your chin in. Slowly round your spine rather than straining your neck.

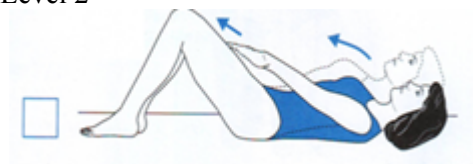
Intensity level 3 – Pelvic tilts and curls with hands behind head. Perform a pelvic tilt, and curl, as before. But with your hands held loosely behind your head.

Appendix 13 (continued)

Level 1



Level 2



Level 3



Shuttle walk or run, or treadmill: in order to improve muscle strengthening, cardiovascular fitness, core-stability, balance and functional rehabilitation

Intensity level 1 – walk at a brisk pace

Intensity level 2 – jog

Intensity level 3 – run

Level 1



Level 2



Level 3



Press-ups: to improve or maintain muscle strength and core-stability mainly for muscles of the chest and arms (Salford Royal Foundation NHS Trust, 2007)

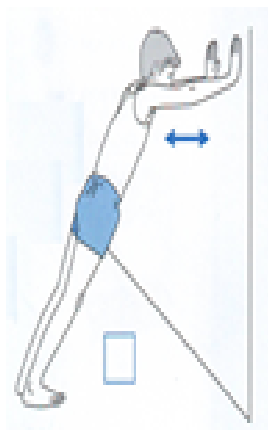
Intensity level one – wall press up. Lean against wall with elbows straight and hands slightly wider apart than shoulder width. Perform a press-up against the wall remembering to tighten your abdominal muscles as you do

Intensity level 2 – box press-up. Start on all fours. Hands under shoulders and knees under hips. Perform a press up in this kneeling position

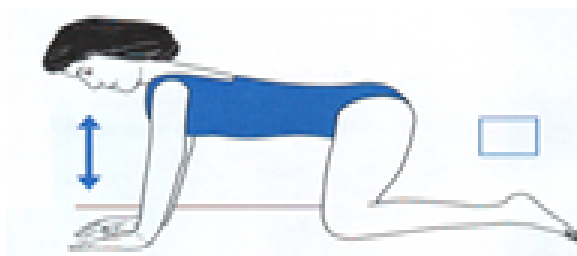
Intensity level 3 – floor press-up. Hands on floor slightly wider apart than shoulder width. Feet shoulder width apart with toes in contact with the floor. Perform a full press-up, remembering to tighten your abdominal muscles as you do so.

Appendix 13 (continued)

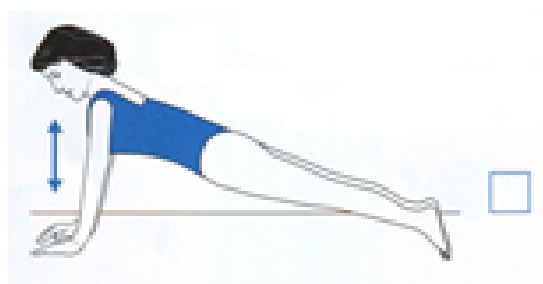
Level 1



Level 2



Level 3



Star steps and jumps: to improve muscle strength, co-ordination, core stability and balance

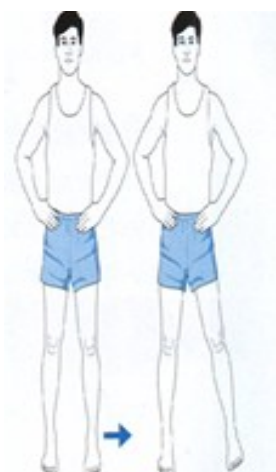
Intensity level 1 – Star steps. Step and touch to the left and right. Hands on hips. Remember to tighten your abdominal muscles.

Intensity level 2 – Star steps with arms. Step and touch to the left and right. At the same time, lift your arms up and down to the sides. Remember to tighten your abdominals.

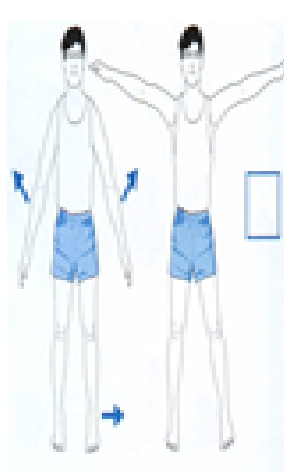
Intensity level 3 – Star jump. Start with feet together and arms down by your sides. Then jump up, land in a star shape, with feet apart and arms outstretched to the side.

Remember to tighten your abdominal muscles.

Level 1



Level 2



Level 3



Appendix 13 (continued)

Arm exercises important in lifting up and carry things through strengthen muscle of arms in order to improve muscle strength and core stability.

Shoulder press

Shoulder fly's

Bicep curls



Step-ups for functional rehabilitation, strengthening and balance (Salford Royal Foundation NHS Trust, 2007)

Intensity level 1 – low step

Intensity level 2 – medium step

Intensity level 3 – high step

Appendix 13 (continued)

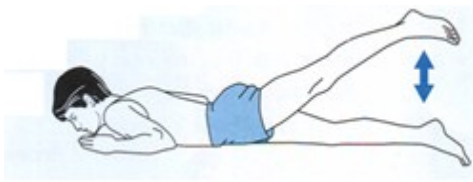
Back exercises to strengthen the muscles of the back

4 to 3 point kneel

4 to 2 point kneel

Supine contralateral leg and arm lift

Level 1



Level 2



Level 3



Appendix 14: Faculty Ethical Approval

MANCHESTER METROPOLITAN UNIVERSITY
FACULTY OF HEALTH, PSYCHOLOGY AND SOCIAL CARE

M E M O R A N D U M

FACULTY ACADEMIC ETHICS COMMITTEE



To: Khamis Yass Chiad Al-Qubaeissy

From: Prof Carol Haigh cc Deirdre Connor

Date: 25 October 2010

Subject: Ethics Application 1029

Title: The long term benefits of Hydrotherapy in early Rheumatoid Arthritis

Thank you for your application for ethical approval.

I have had a look at your response to the issues raised by the reviewers.

The Faculty Academic Ethics Committee review process is now able to recommend approval of your ethics application.

We wish you every success with your project.

J:\Research Degrees Administrator\CONNOR\approvalmemo1029kalqubaeissy25Oct10.doc

Appendix 15: North West NHS 2 Research Ethics Committee- Liverpool Central approval



National Research Ethics Service

North West 2 Research Ethics Committee – Liverpool Central

3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7818
Facsimile: 0161 237 9427

21 October 2010

Mr Khamis AL-QUBAEISSY
PhD student
Manchester Metropolitan University
Elizabeth Gaskell Campus
Hathersage Road
Manchester
M13 0JA

Dear Mr AL-QUBAEISSY

Study Title: Medical Rehabilitation: The long-term benefits of aquatic
Physiotherapy in patients with early Rheumatoid
Arthritis (RA).
REC reference number: 10/H1005/54

Thank you for your letter of 18 October 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, **subject to the conditions specified below.**

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for any non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again if a Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to

This Research Ethics Committee is an advisory committee to North West Strategic Health Authority

*The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England*

Appendix 15 (continued)

the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

- a. The Committee would like to see the Participant Information Sheet revised at point 4 to change the last sentence to "During the trial there is no need to withhold any type of treatment prescribed by your physician."
- b. The Committee would like to see the Letter of Invitation revised to change the sentence "I would like to invite you to participate in this trial to find out what, if any, outcomes for patients with RA following aquatic physiotherapy – also known as hydrotherapy. Please find enclosed patient information for more detailed description of the trial, and a consent form." to "I would like to invite you to participate in this trial to help us find out what, if any, effect aquatic physiotherapy (also known as hydrotherapy) has on patients with RA. Please find enclosed a patient information sheet for a more detailed description of the trial."
- c. The Committee would like to see the Consent Form revised to omit the words "from [company name]" from point 3

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Investigator CV		
Protocol	II	29 September 2010
Academic supervisor CV		
REC application	3.0	23 July 2010
Covering Letter		19 July 2010
Letter from Sponsor		20 June 2010
Questionnaire	EQ-VAS	
Questionnaire	EQ 5D	
Questionnaire: Stanford Health Assessment		
Questionnaire: RADAI patient	final	29 May 2007
Letter of invitation to participant	1	19 July 2010
Letter of invitation to participant	II	29 September 2010

Appendix 15 (continued)

Participant Information Sheet	II	29 September 2010
Response to Request for Further Information		18 October 2010
Participant Consent Form	1	19 July 2010
Participant Consent Form	II	29 September 2010
Questionnaire	RADAI	
Flowchart		
Letter of introduction to colleagues		
Evidence of insurance or indemnity		16 July 2010
Letter from Statistician		06 October 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

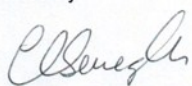
Appendix 15 (continued)

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H1005/54

Please quote this number on all correspondence

Yours sincerely


PP **Professor Sobhan Vinjamuri**
Chair

Email: carol.ebenezer@northwest.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Peter Goodwin*
Lynne Webster
Valerie Edwards-Jones

Appendix 16: Approval letter of CMFT

Central Manchester University Hospitals 
NHS Foundation Trust

Research & Development
1st Floor Post Graduate Centre
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL
Tel: 0161-276-3340
Fax: 0161-276-5766
Lorraine.Broadfoot@cmft.nhs.uk

Ref: R01419-LTR 13-GORODKIN-AMDT 2

Mr Khamis Al-Qubaeissy
PhD Student
Faculty of Health
Manchester Metropolitan University
Elizabeth Gaskell Campus
Hathersage Road
Manchester
M13 0JA

Dear Mr Al-Qubaeissy,

Re: R01419: Medical Rehabilitation: The long-term benefits of aquatic Physiotherapy in patients with early Rheumatoid Arthritis (RA)
REC Reference: 10/H1005/54
Principal Investigator: Dr Rachel Gorodkin
Amendment Number: 2
Amendment Date: 4th March 2011

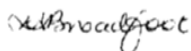
Thank you for your correspondence informing the department of an amendment to the above project, we acknowledge receipt of the following and approve the amendment.

- Ethics Favourable Opinion, dated 8th March 2011
- Consent Form, Version V, dated 28th February 2011
- PIS, Version V, dated 28th February 2011
- Notice of Substantial Amendment, dated 4th March 2011

We have amended the Trust's database to reflect these changes as required.

I would like to take this opportunity to thank you for keeping the Trust informed and wish you continued success with your project.

Yours sincerely



Lorraine Broadfoot
Research Operations Manager

Date: 11th March 2011

cc Dr Rachel Gorodkin

Appendix 17: Approval letter of SRFT



Greater Manchester
Primary Care Research Governance Partnership



NHS SalfoR+D
Acute & Primary Care Research

NHS SalfoR+D Director:
R&D Lead:

Professor Bill Ollier
Rachel Georgiou

SalfoR+D web address:
ReGroup web address:

<http://www.nhssalfordrd.org.uk/>
<http://www.gmregroup.nhs.uk/index.html>

9th August 2011

Mr Khamis Alqubaeissy
PhD student
Manchester Metropolitan University
Elizabeth Gaskell Campus
Hathersage Road
Manchester M13 0JA

Dear Mr Alqubaeissy

Study Title: Medical Rehabilitation: The Long-Term Benefits of Aquatic Physiotherapy in Patients with Early Rheumatoid Arthritis (RA).
REC Reference: 10/H1005/54
EuDraCT Reference: N/A
R&D Reference: 2011/112derm

Thank you for forwarding all the required documentation for your study as above. I am pleased to inform you that your study has been registered with NHS SalfoR+D and has gained NHS R&D approval from the following NHS Trust:

- Salford Royal NHS Foundation Trust

This approval is granted with the proviso that the SSI is signed by Professor Cooper and a copy forwarded to R&D for their records.

All clinical research must comply with the Health and Safety at Work Act, www.hse.gov.uk and the Data Protection Act. <http://www.hmsa.gov.uk/acts>


It is a legal requirement for Principal Investigators involved in Clinical Trials to have completed accredited ICH GCP training within the last 2 years. Please ensure that you provide the R&D Department with evidence of this (certificate for completing the course). A list of GCP training courses can be obtained from the R&D Office.

All researchers who do not hold a substantive contract with the Trust must hold an honorary research contract before commencing any study activities related to this approval. The 'Research Passport Application Form'. This can be obtained from web addresses: <http://www.gmregroup.nhs.uk/researchers/passports.html> and <http://www.hope-academic.org.uk/academic/salfordrd/Research%20Passports.html> This form should be completed and returned, with a summary C.V and recent (within 6 months) CRB to the address shown above.

It is a condition of both NRES and NHS R&D approval that participant recruitment data should be forwarded on a regular basis. Therefore, progress reports must be submitted annually to the

Research & Development Department
Ground Floor, Summerfield House
544 Eccles New Road, Salford M5 5AP

Appendix 18: Ethics statistician letter

University Hospital of South Manchester 
NHS Foundation Trust

Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
M23 9LT

Department of Medical Statistics
Education & Research Centre
Tel: 0161 291 5815

Email: Julie.Morris@manchester.ac.uk

6th October 2010

Re: Medical Rehabilitation: The effects of aquatic physiotherapy in patients with early Rheumatoid Arthritis (RA)

I can confirm that I have assessed the protocol for the above study and have advised that the proposed interim analysis is not appropriate. I have also provided some information relating to a more specific description of a suitable statistical analysis of the data.



Julie Morris
Head of Medical Statistics
University Hospital of South Manchester
Honorary Senior Lecturer
University of Manchester



Appendix 19: Block randomisation of the RCT study (Study One)

Block Randomisation: Method

Each possible permutation of groups A and B in blocks of four was assigned a number (Figure 4). Blocks were repeated to reflect the number of patients in the study (92). A random number sequence was then generated from a computer and was used to choose a particular block, which in turn sets the allocation order for the first four subjects. Numbers in the random number sequence greater than the number of permuted blocks are not used to select blocks (Beller et al, 2002).

The stratified block randomisation process for a block size of four, with A and B being treatment groups (A= land; B= hydrotherapy).

<u>Step 1:</u> <u>Permuted blocks</u>	<u>Step 2:</u> <u>Random number</u> <u>sequence</u>	<u>Step 3:</u> <u>Randomisation list</u>
AABB ABAB BBAA BBAA BABA BAAB AABB ABAB BBAA BBAA BABA BAAB	 1 4 8 6 5 7	A } A } block 1 B } B } B } B } block 4 A } A } A } B } block 8 A } B } B } A } block 6 B } A }

Appendix 20: Shapiro-Wilk tests of normality for hydrotherapy and land groups of RA patients

Variables	Hydrotherapy	Land
HAQ-DI (Test 1)	0.086	0.057
HAQ-DI (Test 2)	0.369	0.087
HAQ-DI (Test 3)	0.101	0.072
HAQ-DI (Test 4)	0.361	0.108
HAQ-VAS (Test 1)	0.068	0.434
HAQ-VAS (Test 2)	0.279	0.213
HAQ-VAS (Test 3)	0.470	0.083
HAQ-VAS (Test 4)	0.163	0.771
HAQ-GWB (Test 1)	0.143	0.741
HAQ-GWB (Test 2)	0.136	0.755
HAQ-GWB (Test 3)	0.068	0.184
HAQ-GWB (Test 4)	0.016*	0.972
EQ-5D _{tariff} (Test 1)	0.022*	0.017
EQ-5D _{tariff} (Test 2)	0.001*	0.006*
EQ-5D _{tariff} (Test 3)	0.011*	0.026*
EQ-5D _{tariff} (Test 4)	0.688	0.545
EQ-5D _{vas} (Test1)	0.131	0.105
EQ-5D _{vas} (Test2)	0.599	0.397
EQ-5D _{vas} (Test3)	0.075	0.236
EQ-5D _{vas} (Test4)	0.516	0.871
RADAI (Test 1)	0.731	0.600
RADAI (Test 2)	0.112	0.949
RADAI (Test 3)	0.757	0.367
RADAI (Test 4)	0.272	0.576
DAS28 (Test 1)	0.055	0.721
DAS28 (Test 2)	0.065	0.938
DAS28 (Test 3)	0.069	0.380
DAS28 (Test 4)	0.377	0.251
HADS (Test 1)	0.147	0.051
HADS (Test 2)	0.018*	0.024*
HADS (Test 3)	0.383	< 0.001
HADS (Test 4)	0.693	0.204
HAD-D (Test 1)	0.527	0.010*
HAD-D (Test 2)	0.105	0.020*
HAD-D (Test 3)	0.290	0.198
HAD-D (Test 4)	0.410	0.326
HAD-A (Test 1)	0.787	0.022*
HAD-A (Test 2)	0.034*	0.022*
HAD-A (Test 3)	0.712	0.720
HAD-A (Test 4)	0.511	0.485

Keys: *statistically significant at $p < 0.05$ indicate non-normally distributed for data
 Bold face ($p > 0.05$ = not statistically significant) refers to normally distributed data

Appendix 21: Within group comparison of outcome measures at Test 1, 2 and 3 in the both groups (n = 14).

Variables	p values	Variables	p values
Land group		Hydrotherapy group	
HAQ-DI [†]	0.626	HAQ-DI [†]	0.003
HAQ _{VAS} [†]	0.441	HAQ _{VAS} [†]	0.004
HAQ-GWB [†]	0.147	HAQ-GWB [†]	0.002
EQ-5D tariff*	0.798	EQ-5D tariff*	0.839
EQ-5D _{VAS} [†]	0.095	EQ-5D _{VAS} [†]	0.009
RADAI [†]	0.792	RADAI [†]	0.568
HADs*	0.266	HADs*	0.199
HAD-D*	0.746	HAD-D*	0.259
HAD-A*	0.612	HAD-A*	0.613
<p>†Values were measures by repeated measures ANOVA</p> <p>*values were measured by Friedman test</p> <p>Significant p values set at 0.017 are indicated in boldface</p> <p>Key:</p> <p>HAQ-DI overall scores (0 to 3), with 0 being best and 3 worst functioning</p> <p>HAQ_{VAS} score (0-100), 0 = no pain, 100 = severe pain</p> <p>HAQ GWB scores (0 – 100), 0 = very well, 100 = very poor</p> <p>EQ-5D tariff score (- 0.594 to 1), with 1= perfect health, - 0.594 worse than death</p> <p>EQ-5D_{VAS} score (0-100), with 0 low quality and 100 high quality</p> <p>RADAI overall score (0 – 10), with 0 no disease activity and 10 very severe</p> <p>DAS28 overall score (0 -9.4), with 0 no disease activity and 9.4 very severe</p> <p>HAD overall score (zero – 42), with zero (no depression, anxiety), 42 (very severe depression, anxiety)</p> <p>HAD-D overall score (0-21), with 0-7 normal, 8-10 borderline case, ≥ 11 definite</p> <p>HAD-A overall score (0-21), with 0-7 normal, 8-10 borderline case, ≥ 11 definite</p>			

Appendix 22: HAQ-DI categories between hydrotherapy and land group at Test 2.

HAQ-DI categories	Hydrotherapy (n = 21) Mean (SD)	Land therapy (n = 22) Mean (SD)	p (95% CI)
Dressing & Grooming	1.1 (0.8)	1.3 (1)	0.40 (- 0.31 to 0.76)
Arising	1 (0.7)	1 (0.8)	0.062 (- 0.88 to 0.02)
Eating	1 (0.6)	1.3 (0.8)	0.23 (- 0.2 to 0.7)
Walking	0.9 (0.9)	1.3 (1)	0.2 (- 0.2 to - 1.1)
Hygiene	1.3 (1.1)	1.5 (1)	0.44 (- .41 to 0.92)
Reach	1.2 (0.9)	1.7 (1)	0.13 (- 0.14 to 1.1)
Grip	1.4 (0.7)	1.4 (0.9)	0.91 (- 0.55 to 0.5)
Activities	1.3 (1)	1.6 (1)	0.34(- 0.33 to 0.95)
Key: HAQ-DI overall scores (0 to 3), with 0 being best and 3 worst functioning			

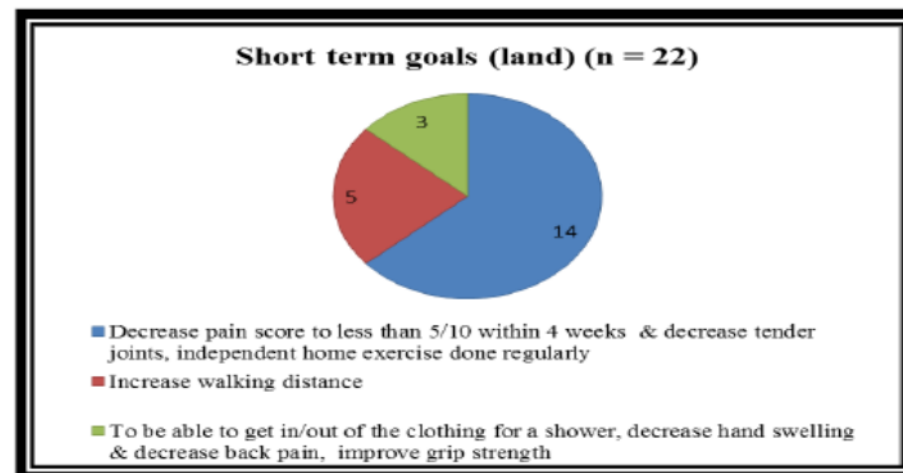
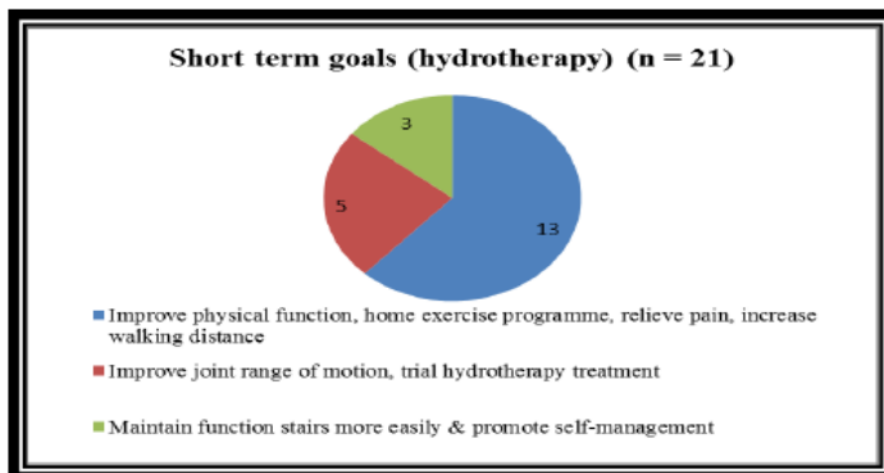
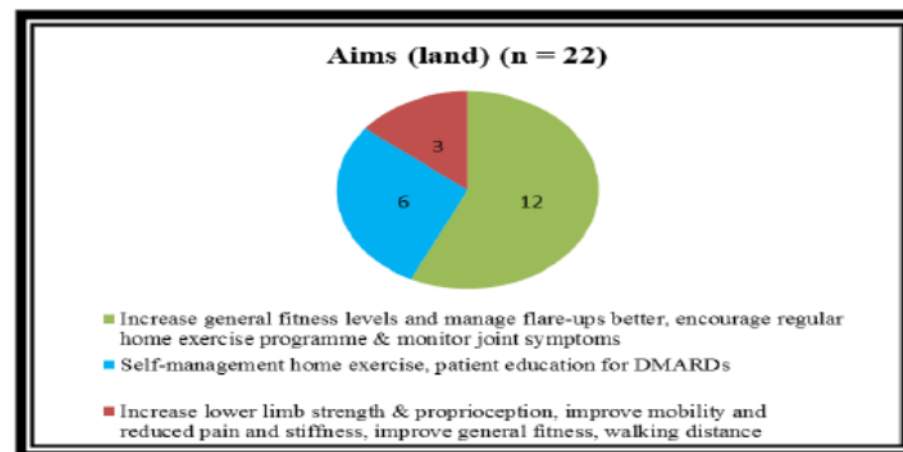
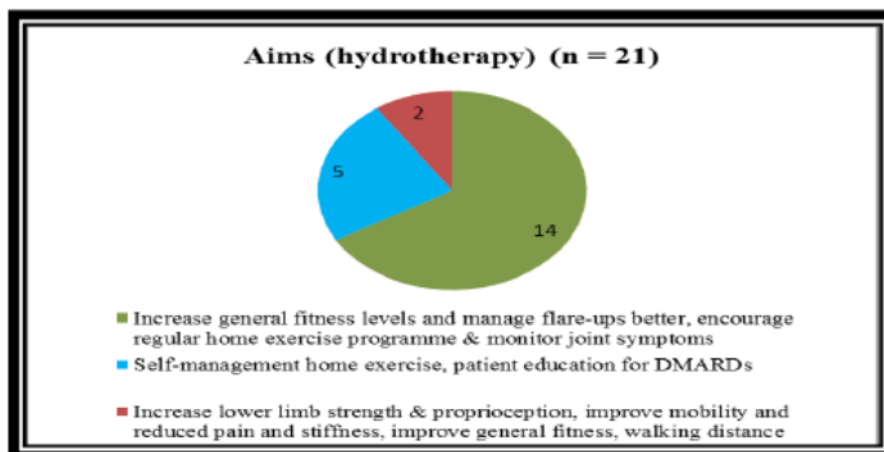
Appendix 23: Comparison of outcome measures for difference in change score between groups (Test 1 and 3).

Variables	Hydrotherapy (n = 14)	Land (n = 14)	p (95% CI)
Primary outcome measure			
Functional ability			
HAQ-DI [†]	0.52 (0.81)	0.14 (0.71)	0.217 (- 0.97 to 0.23)
Secondary outcome measure			
HAQ _{VAS} [†] (Pain)	15.2 (25.8)	- 19 (24.5)	0.124 (- 35.4 to 4.6)
HAQ-GWB [†] (Wellbeing)	15.1 (25.15)	2.2 (19.4)	0.149 (- 30.9 to 5)
Health status (QoL)			
EQ-5D tariff*	0 (0.35)	0 (0.22)	0.329
EQ-5D _{VAS} [†]	- 14 (26)	- 19 (33)	0.686 (- 28 to 19)
Disease activity			
RADAI [†]	0.13 (3.1)	- 0.1 (2.2)	0.824 (- 2.38 to 1.9)
DAS28 [†]	1.4 (1.8)	0.37 (2.1)	0.189 (- 2.5 to 0.53)
Mood symptoms			
HAD scale *	0.5 (10.5)	- 2 (9.5)	0.350
HAD-D *	0.5 (5.5)	0 (4. 5)	0.830
HAD-A *	1 (5.5)	1 (4)	0.793
[†] Values are in mean (SD) and by independent t-test *values in median (IQR) and by Mann-Whitney U test Significant p values are indicated in boldface Key: HAQ-DI overall scores (0 to 3), with 0 being best and 3 worst functioning HAQ _{VAS} score (0-100), 0 = no pain, 100 = severe pain HAQ GWB scores (0 – 100), 0 = very well, 100 = very poor EQ-5D tariff score (- 0.594 to 1), with 1= perfect health, - 0.594 worse than death EQ-5D _{VAS} score (0-100), with 0 low quality and 100 high quality RADAI overall score (0 – 10), with 0 no disease activity and 10 very severe DAS28 overall score (0 -9.4), with 0 no disease activity and 9.4 very severe HAD overall score (zero – 42), with zero (no depression, anxiety), 42 (very severe depression, anxiety) HAD-D overall score (0-21), with 0-7 normal, 8-10 borderline case, ≥ 11 definite HAD-A overall score (0-21), with 0-7 normal, 8-10 borderline case, ≥ 11 definite			

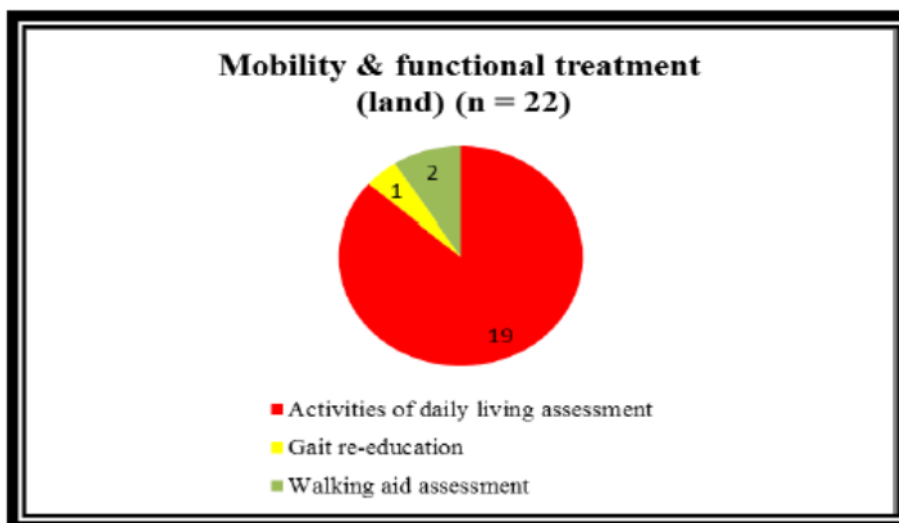
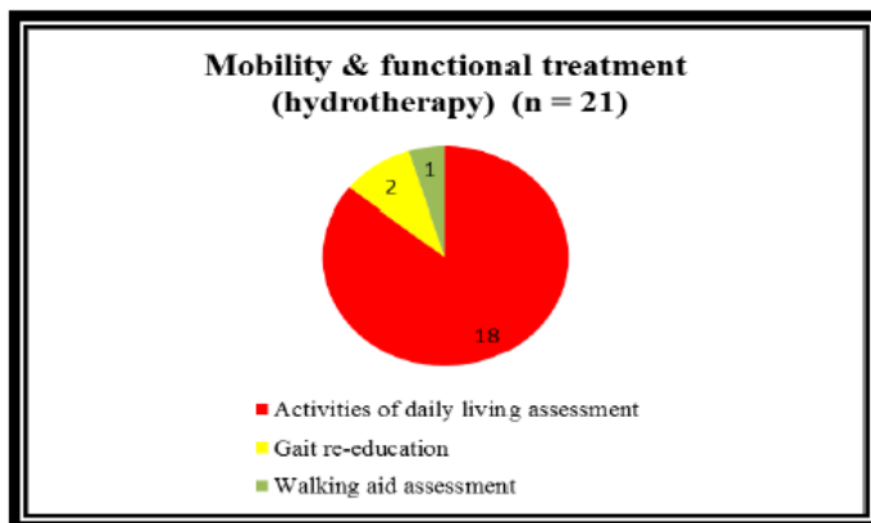
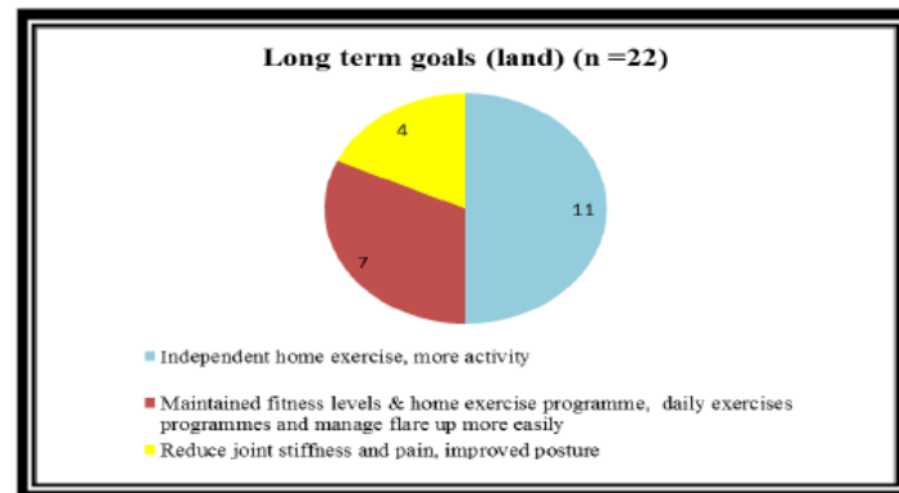
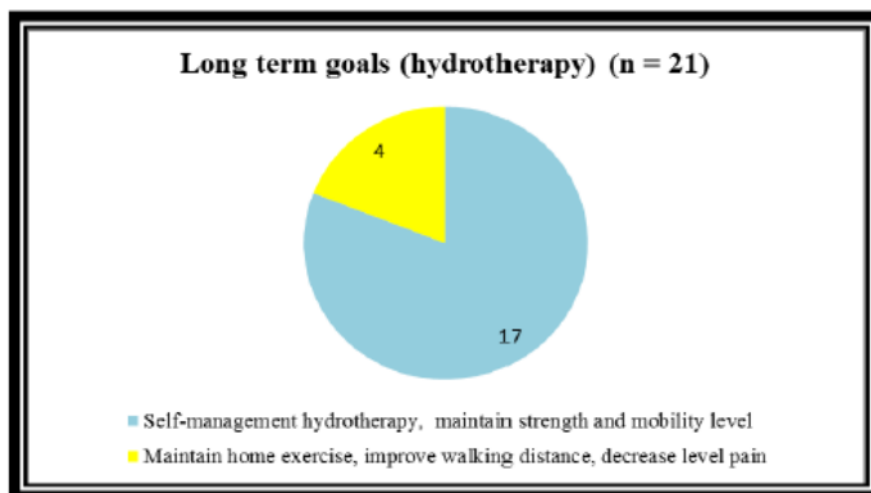
Appendix 24: Comparison of outcome measures for difference in change score between groups (Test 2 and 3).

Variables	Hydrotherapy (n = 14)	Land (n = 14)	p (95% CI)
Primary outcome measure			
Functional ability HAQ-DI [†]	- 0.12 (0.46)	- 0.12 (0.48)	0.999 (- 0.37 to 0.37)
Secondary outcome measure			
HAQ _{VAS} [†] (Pain)	15.3 (25.8)	- 0.19 (24.5)	0.124 (- 35.4 to 4.6)
HAQ-GWB [†] (Wellbeing)	15.2 (25.8)	2.2 (19.4)	0.148 (- 30.9 to 5)
Health status (QoL)			
EQ-5D tariff*	0 (0.18)	0 (0.29)	0.941
EQ-5D _{VAS} [†]	7.4 (22)	- 17 (27.6)	0.057 (- 44 to - 4.8)
Disease activity			
RADAI [†]	- 0.49 (2.4)	0.25 (2.2)	0.418 (- 1.1 to 2.6)
DAS28 [†]	- 0.32 (1.45)	- 0.80 (1.5)	0.385 (- 1.6 to 0.65)
Mood symptoms			
HAD scale *	- 1.5 (6.5)	0 (6)	0.436
HAD-D *	- 1 (3.5)	0 (4)	0.714
HAD-A *	0 (4.5)	1 (6)	0.118
[†] Values are in mean (SD) and by independent t-test *values in median (IQR) and by Mann-Whitney U test Significant p values are indicated in boldface Key: HAQ-DI overall scores (0 to 3), with 0 being best and 3 worst functioning HAQ _{VAS} score (0-100), 0 = no pain, 100 = severe pain HAQ GWB scores (0 – 100), 0 = very well, 100 = very poor EQ-5D tariff score (- 0.594 to 1), with 1= perfect health, - 0.594 worse than death EQ-5D _{VAS} score (0-100), with 0 low quality and 100 high quality RADAI overall score (0 – 10), with 0 no disease activity and 10 very severe DAS28 overall score (0 -9.4), with 0 no disease activity and 9.4 very severe HAD overall score (zero – 42), with zero (no depression, anxiety), 42 (very severe depression, anxiety) HAD-D overall score (0-21), with 0-7 normal, 8-10 borderline case, ≥ 11 definite HAD-A overall score (0-21), with 0-7 normal, 8-10 borderline case, ≥ 11 definite			

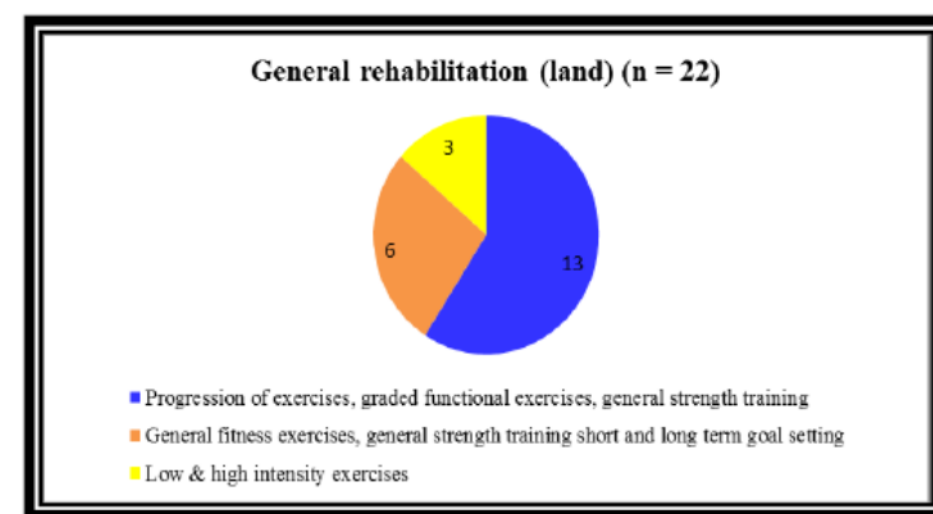
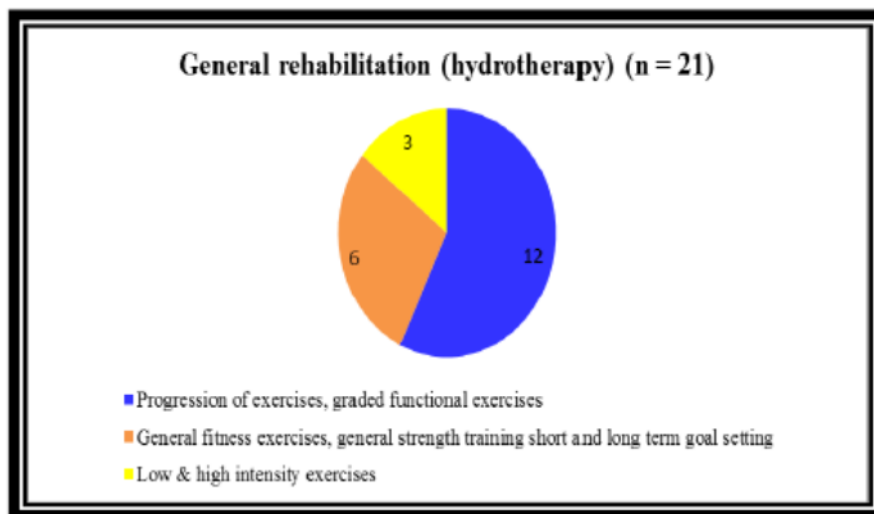
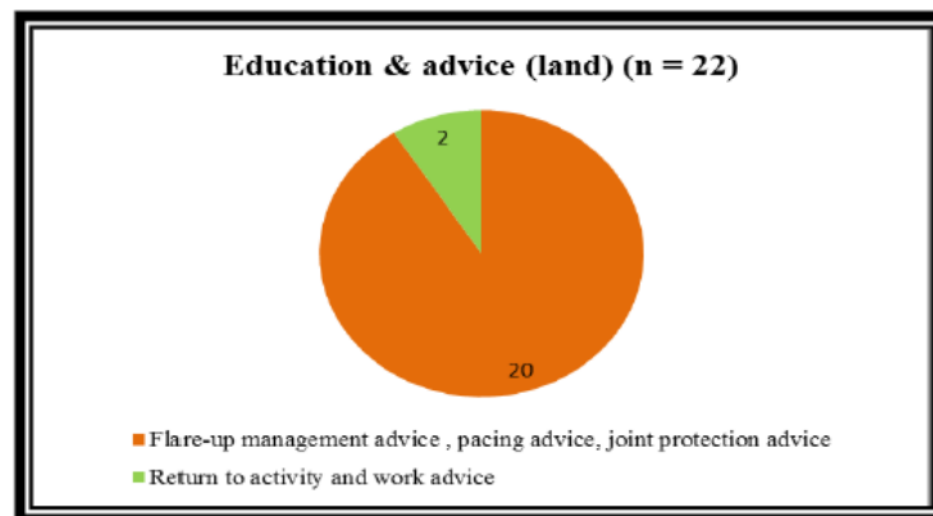
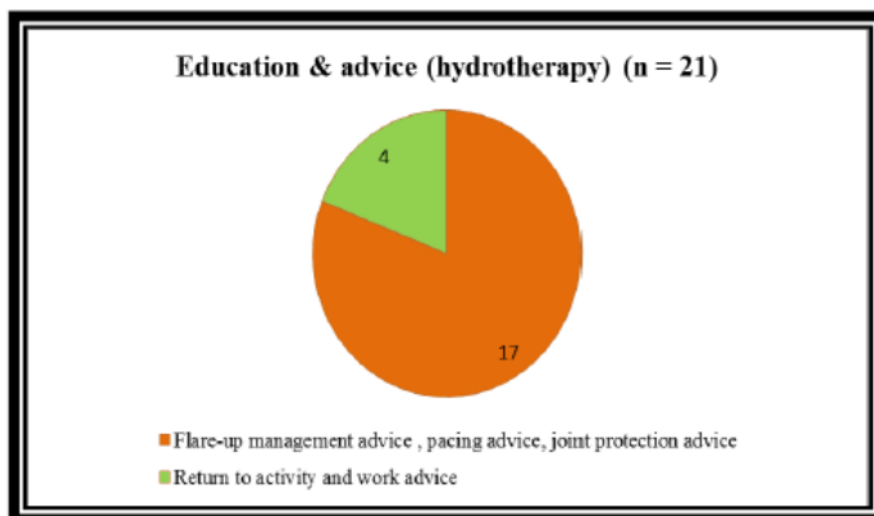
Appendix 25: Exercise Pie chart



Appendix 25 (continued)

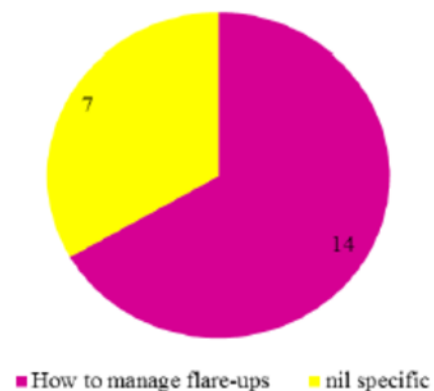


Appendix 25 (continued)

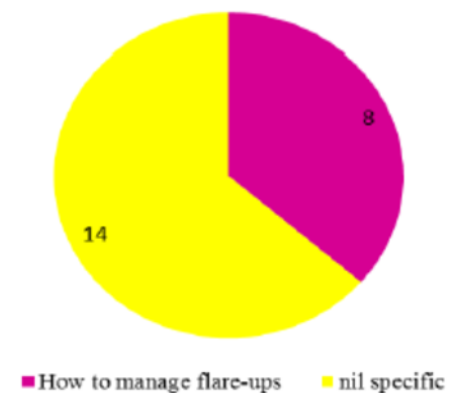


Appendix 25 (continued)

Pain relief (hydrotherapy) (n = 21)



Pain relief (land) (n = 22)



Home Exercise Programme(hydrotherapy) (n = 21)

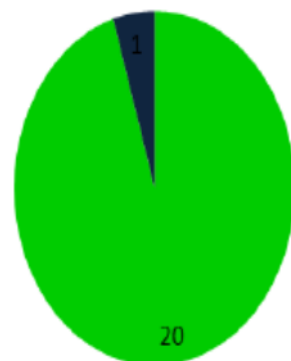


Home Exercise Programme (land) (n = 22)



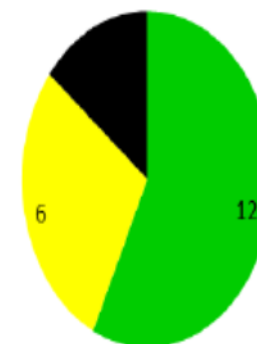
Appendix 25 (continued)

Hydrotherapy exercises (hydrotherapy) (n = 21)



- Range of movement, sustained stretches, core stability exercises, balance exercises
- Range of movement, core stability exercises, balance exercises

Land exercise (land) (n = 22)



- Range of movement, strengthening, fitness exercises, gym-based group exercise
- Range of movement, strengthening, fitness exercises
- Range of movement, strengthening, gym-based group exercise

Appendix 26: Kellgren Rheumatology Outpatient data form of Study Two

Rheumatology Outpatient Data Form

Version I

Date 14/04/2011

Age of patient:	
Gender:	
Duration of disease [date of diagnosis]:	
Occupation status:	
Height, weight and body mass index (BMI)	
DAS28 if recorded	
Marital status:	
Hypertension	
Smoking	
Rheumatoid Factor	
Current treatment [drug regimens]:	
Comorbidity (other illnesses)	

Appendix 27: Covering information letter to the Kellgren participants (Study Two)



Covering information letter

Version I

Date: 17/06/2011

Project Title: Medical rehabilitation: the effects of aquatic physiotherapy in patients with Rheumatoid Arthritis (RA).

We would be grateful if you would take the time to read the following information carefully. Feel free to talk to others about it if you wish.

Background

Researchers at the Kellgren Centre and Manchester Metropolitan University are working together on a study looking at the effects of aquatic physiotherapy (hydrotherapy) in patients with RA. There are over 2000 patients with RA attending the Kellgren Centre and a proportion of those are referred to aquatic physiotherapy at Manchester Royal Infirmary (MRI).

Aim

As part of the larger study, we would like to carry out a smaller one. We are trying to see if those patients with RA referred to aquatic physiotherapy have different characteristics to those who do not. We think this is important because it will enable doctors and physiotherapists to look out for those patients who are likely to need aquatic physiotherapy and provide a more efficient service.

Plan

In order to carry out this study we plan to gather information from a sample of 10% (200) of all patients at the Kellgren Centre. You will not have to do anything as all the information can be obtained from medical notes. The notes will be chosen at random so you may or may not be involved. Researchers will not know whose information is being used because no names or any other patient identifiable information will be used.

Information will include no more than:

Age

Gender

Duration of disease [date of diagnosis]

Occupation status [e.g. retired / working]

Comorbidities

Current treatment [drug regimens]

Height

Weight

Disease Activity Score [DAS] 28 [if recorded]

We are working together with the support of your clinical team. The research nurse [Lindsey Barnes] at the Kellgren Centre will select the notes from those on clinic days and fill in the above information for the researchers. Medical notes will not leave the Kellgren Centre nor will anyone have access to the notes other than your consultant and nurse.

Appendix 27 (continued)

Only the above data will be transferred to the University and then stored on computers with passwords in lockable rooms. The information will be grouped together and only averages of all the data will be reported, so individual characteristics will not be described. The lead researcher will look at some parts of the data collected for the study; authorised people may also look at them from Central Manchester University Hospitals NHS Foundation Trust to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

Because we think that this is important, we hope to publish the findings in a medical journal.

- You do not need to do anything if you are happy for your information to be used should it be selected.
- If you would not like your information to be used should it be chosen or if you would like any further information about the study, please contact the Researcher, below.

Researcher contact details:

Khamis AL-Qubaeissy, Doctoral Researcher/Medical Rehabilitation,

Elizabeth Gaskell Campus, Hathersage Road,
Manchester. M13 0JA

Tel: 01612472610

Email: 09981701@stu.mmu.ac.uk

Yours sincerely,

Khamis AL-Qubaeissy, Doctoral Researcher/Medical Rehabilitation

Appendix 28: Letter from clinicians in the Kellgren Centre (Study Two)

1 August 2011

Chairman

National Research Ethics Service

North West 2 Research Ethics Committee-Liverpool Central

3rd Floor

4 Minshull Street

Manchester

M1 3DZ

Dear Ethics Committee:

Re: Study Title: Medical Rehabilitation: the effects of aquatic physiotherapy in patients with Rheumatoid Arthritis (RA).

This letter is to confirm that the clinical team at the Kellgren Centre, MRI are happy to collaborate in the above study.


We agree to provide administrative support via our research nurse, Lindsey Barnes (who is part of our clinical team and routinely sees our patients). Patients would be sent a letter informing them that their clinical data may be used anonymously and giving them the opportunity to object and have their data withdrawn from the study. Anonymous data would then be provided to the researchers at Manchester Metropolitan University.

Yours sincerely,

Drs Rachel Gorodkins and Pauline Ho
Consultant Rheumatologists
Kellgren Centre for Rheumatology

Lindsey Barnes
Research Nurse
Kellgren Centre for Rheumatology

Appendix 29: North West NHS 2 Research Ethics Committee- Liverpool Central approval letter of Study Two


National Research Ethics Service
NRES Committee North West - Liverpool Central
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ
Tel: 0161 625 7816

10 August 2011

Mr Khamis Al-Qubaeissy
PhD student
Manchester Metropolitan University
Elizabeth Gaskell Campus
Hathersage Road
Manchester
M13 0JA

Dear Mr Al-Qubaeissy

Study title: Medical Rehabilitation: The long-term benefits of aquatic
Physiotherapy in patients with early Rheumatoid Arthritis
(RA).

REC reference: 10/H1005/54

Amendment number: Modification of amendment 3

Amendment date: 08 August 2011

Thank you for submitting the above amendment, which was received on 08 August 2011. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter of 16 May refers).

The modified amendment was reviewed by the Sub-Committee in correspondence. A list of the members who took part in the review is attached.

Ethical opinion

I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved are:

Document	Version	Date
Letter from responsible clinicians		01 August 2011
Rheumatology Outpatient Data Form	1	14 April 2011
Participant Information Sheet	1	17 June 2011
Modified Amendment - Modification of amendment 3		08 August 2011
Covering Letter		01 August 2011

This Research Ethics Committee is an advisory committee to the North West Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England

Appendix 29 (Continued)

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

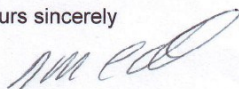
Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

10/H1005/54:

Please quote this number on all correspondence

Yours sincerely



PP

Professor Sobhan Vinjamuri
Chair

E-mail: diane.catterall@northwest.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Peter Goodwin
Dr Lynne Webster, Central Manchester University Hospital NHS
Foundation Trust*

NRES Committee North West - Liverpool Central

Attendance at Sub-Committee of the REC meeting on 09 August 2011

Name	Profession	Capacity	
Mrs Julie Brake	Specialist Diabetes Nurse / Vice Chair	Expert	
Professor Sobhan Vinjamuri	Consultant in Nuclear Medicine	Expert	

Appendix 30: Patient costs questionnaire 1

Study Title: The effect of aquatic physiotherapy in patients with Rheumatoid Arthritis



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We are interested in how people travel to hospital and the costs they incur for patients who have RA and who are currently attending or have recently attended hydrotherapy or land-based therapy. Would you please return the completed questionnaire to Khamis Al-Qubaeissy and his address is below.

The information you provide will be treated in complete confidence and will not affect the service you receive. Thank you for your help.

Khamis Al-Qubaeissy
PhD Student
Manchester Metropolitan University
Elizabeth Gaskell Campus
Hathersage Road
Manchester M13 0JA
Tel: 0161 2472610

Appendix 30 (continued)

We would like you to think about the journey you made to attend your hydrotherapy.

1a. How did you travel to and from the hospital?
(You may tick more than one box, if appropriate)

	Car	Bus or train	Taxi	Walk	Ambulance	Other
Journey to Hospital	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Journey From Hospital	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

1b. If you ticked 'Other' Please specify.....

.....

1c. If you ticked 'bus or train, or 'taxi', please indicate the approximate return fare:

£.....

1d. Are you eligible for reimbursement for the costs you have incurred in attending this appointment.

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

Appendix 30 (continued)

2. How long was the journey from home to hospital? Please give the approximate time from door to door:

..... HoursMinutes

3. Approximately how far did you travel from home to the hospital?

.....Miles

4. If you came by car, how much have you had to pay for parking?

£.....

Yes No

5. Did someone accompany you to the hospital?

☐ ☐

Yes No

6. If you were accompanied, did your companion also have an appointment at the hospital?

☐ ☐

7a. What would you (and your companion, if relevant) normally have been doing had you not had to visit the hospital? *(Please tick the appropriate boxes).*

	Self	Companion
Paid Occupation		
Looking after children, other relatives, friends		
Other (please describe)		

Appendix 30 (continued)

7b. If you have ticked 'Paid Occupation' above, please indicate what arrangements you made to be absent from work. *(Please tick the appropriate boxes).*

	Self	Companion
Annual Leave		
Hours Rearranged		
Time Off <u>Without</u> Loss of Pay		
Time Off <u>With</u> Loss of Pay		
Other (please describe)		

7c. If you have ticked 'Time off with Loss of Pay'
Please indicate the approximate sum you have lost.

£.....

8a. Were there any other costs involved in visiting the hospital, which have not been covered above? If so, please give details.

.....
.....

8b. What was the total cost incurred by these other expenses?

£.....

9. Please give the total time, in minutes, spent at the hospital on this visit (excluding travelling time).

.....Minutes

Appendix 31: Patient Costs Questionnaire 2

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Patient Costs Questionnaire (all Patients after 6 weeks of intervention)

Have you visited your GP about your RA after 6 weeks of aquatic therapy?
Yes / No

If YES, how many times?

How much did you spend on travel and prescription charges in total?

£ _____

Have you attended any therapy sessions other than hydrotherapy for your RA?

Yes / No

If YES, what type of therapy was it?

How many sessions did you attend?

How much did you spend on travel and therapy charges in total?

£ _____

Appendix 32: The hospital physiotherapist costs (Adapted from Curtis, 2011)

Unit estimation and costs	2010 / 2011	Notes
A. Wages /salary	£22,700 per year	Based on the median full-time equivalent basic salary for Agenda for Change Band 5 of the January - March 2011 NHS Staff Earnings for qualified Allied Health Professionals. Median full-time equivalent total earnings, which include basic salary plus hours-related pay, overtime, occupation payments, location payments, and other payments such as redundancy pay or payment of notice periods, were £24,100 (The Information Centre for health and social care, 2011). More specialist grades range from AfC band 6 to 8C for a physiotherapist specialist to consultant.
B. Salary oncosts	£5,352 per year	Employers' national insurance plus 14 % of salary for employers' contribution to superannuation
C. Qualifications	£4,927 per year	The equivalent annual cost of pre-registration education after the total investment cost has been annuitized over the expected working life (Netten et al., 1998). The Department of Health and the Higher Education Funding Council have provided current cost information for England (HEFCE).
D. Overheads Management, administration and estates staff Non-staff	£5,330 per year £11,782 per year	Taken from NHS (England) Summarised Accounts (National Health Service Act 2006, 2010) Management and other non-care staff costs were 19.1 % of direct care salary costs and included administration and estates staff. Non-staff costs were 41.6 per cent of direct care salary costs. They include costs to the provider for office, travel/transport and telephone, education and training, supplies and services (clinical and general), as well as utilities such as water, gas and electricity.
E. Capital overheads	£4,541 per year	Based on the new-build and land requirements of NHS facilities, but adjusted to reflect shared use of both treatment and non-treatment space (Building Cost Information Service, 2011; Department for communities and local government, 2011). No allowance has been made for the cost of equipment. Capital costs have been annuitised over 60 years at a discount rate of 3.5%
F. Travel		No information available on average mileage covered per visit. Current guideline for reimbursement: 54 pence per mile up to 3,500 miles, 18 pence over 3,500 miles (NHS Employers, 2012 a)
Working time	41.3 weeks per annum 37.5 hours per week	Includes 29 days annual leave and 8 days statutory leave (NHS Employer, 2012 b). Assumes 5 study/training days and 12 days sickness leave (The Information Centre for health and social care, 2021). Unit costs based on 1549 hours per annum.
Ratio of direct to indirect time		No current information available.
Duration of contacts	32.9 minutes 23.3 minutes 13.1 minutes	Surgery consultation. Clinic consultations. Telephone consultations. All based on information taken from the 2006/07 General Practice Workload Survey (The Information Centre knowledge for care, 2007)
Non-London multiplier	0.97 x E	Allows for the lower costs associated with working outside London compared to the national average cost (Building Cost Information Service, 2011; Department for communities and local government, 2011).
Unit costs available 2010/2011 (costs including qualifications given in brackets)		
£32 (£35) per hour.		

Appendix 33: The hospital physiotherapist assistant costs (Adapted from Curtis, 2011)

Unit estimation and costs	2010 / 2011	Notes
A. Wages /salary	£17,600 per year	Based on the median full-time equivalent basic salary for Agenda for Change Band 3 of the January-March 2011 NHS Staff Earnings estimates for unqualified allied health professionals. Median full-time equivalent total earnings, which include basic salary plus hours-related pay, overtime, occupation payments, location payments, and other payments such as redundancy pay or payment of notice periods, were £18,400(The Information Centre for health and social care, 2011).
B. Salary oncosts	£3,985 per year	Employers' national insurance is included plus 14 per cent of salary for employers' contribution to superannuation.
C. Qualifications	£0	Training costs are assumed to be zero, although many take NVQ courses.
D. Overheads Management, administration and estates staff Non-staff	 £4,123 per year £8,979 per year	 Taken from NHS (England) Summarised Accounts. (National Health Service Act 2006, 2010) Management and other non-care staff costs were 19.1 per cent of direct care salary costs and included administration and estates staff. Non-staff costs were 41.6 per cent of direct care salary costs. They include costs to the provider for office, travel/transport and telephone, education and training, supplies and services (clinical and general), as well as utilities such as water, gas and electricity.
E.Capital overheads	£2,970 per year	Based on the new-build and land requirements of NHS facilities, but adjusted to reflect shared use of both treatment and non-treatment space (Building Cost Information Service, 2011; Department for communities and local government, 2011). Capital costs have been annuitised over 60 years at a discount rate of 3.5 per cent.
Working time	42.3 weeks per annum 37.5 hours per week	Includes 29 days annual leave, 8 days statutory leave and 12 days sickness leave (NHS Employer, 2012 b; The Information Centre for health and social care, 2021). No study/training days have been assumed. Unit costs based on 1585 hours per annum
Ratio of direct to indirect time		No current information available.
Non-London multiplier	0.97 x E	Allows for the lower costs associated with working outside London compared to the national average cost (Building Cost Information Service, 2011; Department for communities and local government, 2011).
Unit costs available 2010/2011		
£24 per hour		

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